



Original article

# Trends in mortality of adult patients diagnosed with myeloid leukemia from 1994 to 2011 in southeastern Brazil



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ABSTRACT

**Objective:** To evaluate trends in mortality among adults with myeloid leukemia in the Vale do Paraíba, State of São Paulo.

**Methods:** Data from the Brazilian National Health Service database DATASUS provided the number of deaths caused by myeloid leukemia and the number of inhabitants per year in the Regional Health Division XVII from 1994 to 2011. Registries were categorized according to gender into four age ranges (over 20 years, 20–49, 50–69 and over 70 years) for an estimation of the annual percent change for age-adjusted mortality rates. The percent changes were calculated using the Joinpoint regression analysis model.

**Results:** Overall, a significant decline per year was demonstrated for the entire sample (over 20 years) across the 18-year period studied (annual percent change: –5.59%; 95% CI: –8.5 to –2.5% for males;  $p$ -value < 0.05 and –7.02%; 95% CI –11.2 to –2.8% for females;  $p$ -value < 0.05) with no significant difference between genders. In an analysis using two Joinpoints, significant drops were observed from 1994 to 2001 (annual percent change: –21.22%; 95% confidence interval: –27.9 to –13.9%;  $p$ -value < 0.05) and from 1994 to 2003 (annual percent change: –12.86%; 95% confidence interval –22.2 to –2.5%;  $p$ -value < 0.05) for men and women, respectively. The declining trends were greatest for patients aged over 70 years with the age-adjusted mortality rates in younger groups declining non-significantly except for males aged 50–69 years old.

**Conclusion:** Our data suggest a significant decline per year in age-adjusted mortality rates of adult patients diagnosed with myeloid leukemia from 1994 to 2011 in the Vale do Paraíba, State of São Paulo.

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## Introduction

It is widely accepted that the assessment of mortality data is a useful tool for monitoring outcomes in patients with hematologic malignancies, particularly in countries where survival estimates from cancer registries are not broadly available.<sup>1,2</sup> This information may be relevant to the strategic planning of health managers and enable the implementation of measures to improve services that treat these kinds of diseases.

Myeloid leukemia is a group of hematologic malignancies divided into acute and chronic subtypes, some of which require expensive treatment regimens while others are potentially lethal. In Brazil, the Ministry of Health has demonstrated the mortality rates for leukemia in general<sup>3</sup> but there are insufficient data to support discussions regarding death rates from myeloid leukemia.

Therefore, in order to provide comprehensive and regionalized information which reflect the characteristics and needs of the local population, an exploratory analysis of the mortality trends due to myeloid leukemia was performed in the Vale do Paraíba, State of São Paulo.

## Methods

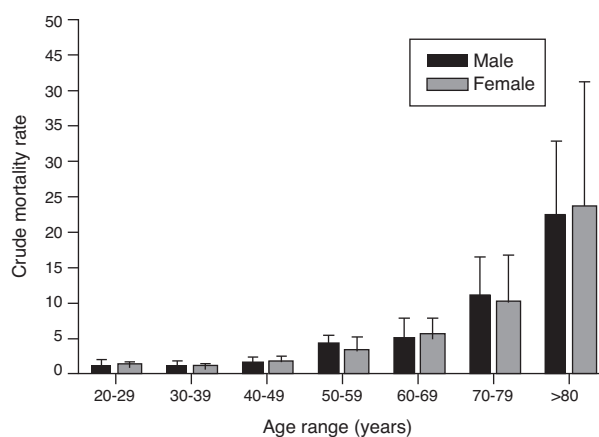
This study was carried out in the Centro de Hematologia do Vale (CHV). The CHV consists of medical oncohematological professionals from the following services: Pio XII Hospital in São José dos Campos and the Regional Hospital of the Vale do Paraíba, located in the city of Taubaté. These non-teaching hospitals are referral centers of the Regional Health Division XVII, composed of 39 municipalities in the Vale do Paraíba. They have treated patients with hematologic malignancies under the Brazilian National Health Service (SUS) since early 1999. Together, the services that comprise the CHV attend all adult SUS patients diagnosed with acute myeloid leukemia (AML) and more than 110 patients with chronic myeloid leukemia (CML).

Data from the SUS database, DATASUS (Health Information, TABNET, statistical data), available on the Brazilian Ministry of Health website<sup>4</sup> were considered for inclusion in the analysis. Registries from the Regional Health Division XVII (Vale do Paraíba), provided the number of deaths per year due to myeloid leukemia (categorized as C92 according to the International Classification of Diseases 10 [ICD-10] from 1996 to 2011 and as 205 according to ICD-9 from 1994 to 1995). This classification comprises the following diseases: AML, CML, subacute myeloid leukemia, acute promyelocytic leukemia (APL), acute myelomonocytic leukemia, myeloid leukemia otherwise specified and myeloid leukemia not otherwise specified. To obtain a set of data with adequately specified characteristics, registries were grouped according to gender into seven age ranges: 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and more than 80 years. Registries (Health Information, TABNET, demographic and socioeconomic data) also provided the number of residents per year according to the above-mentioned age ranges and the 2000 standard million population; thus the death rates per 100,000 inhabitants were calculated (crude mortality rate). These groups were

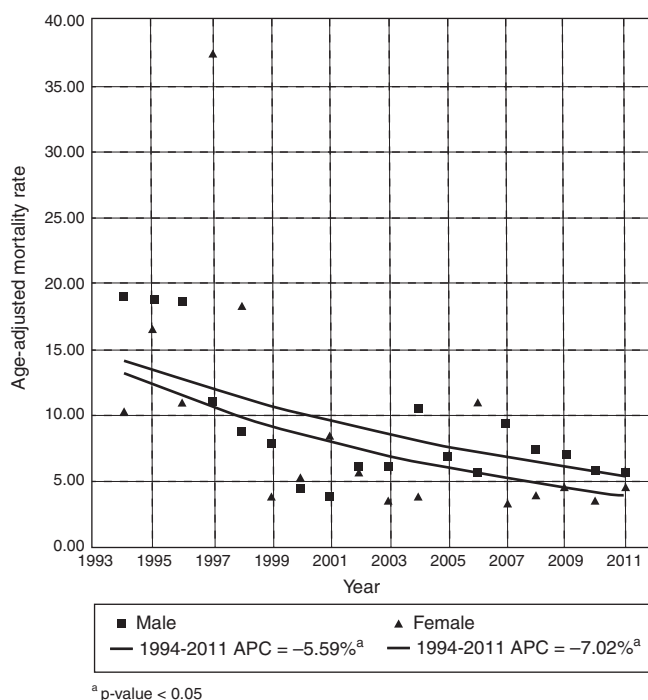
compared using the one-way analysis of variance (ANOVA), and Kruskal–Wallis test with Dunn's multiple comparisons test. *p*-values less than 0.05 were considered statistically significant. The annual percent change (APC) of the age-adjusted mortality rates based on the 2000 standard million population was also estimated by fitting a straight-line regression to the natural logarithm of the rates, with calendar year used as a regressor variable in Joinpoint regression analysis<sup>5</sup> using the Joinpoint Regression Program (version 4.0.4).<sup>6</sup> The APC were considered significant when the 95% confidence intervals (95% CI) excluded zero (*p*-value < 0.05). In order to compare the data, the same method was adapted to perform APC analysis of age-adjusted mortality rates among patients with myeloid leukemia from all regions of Brazil.

## Results

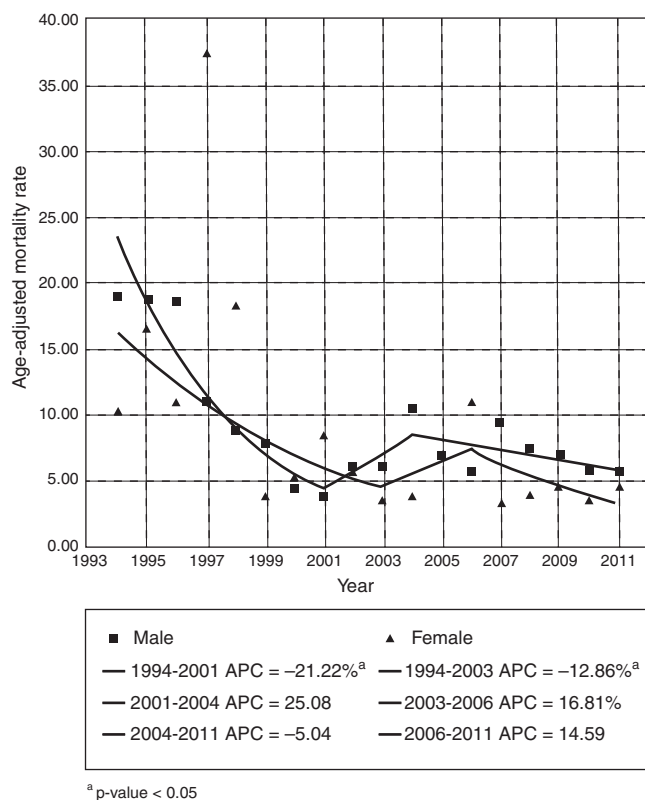
The crude mortality rate rose as the age increased with this phenomenon being observed equally in men and women; similar crude mortality rates were found between 20 and 49 years, 50 and 69 years and over 70 years (Figure 1). Based on these initial findings, data were categorized according to gender into four age ranges (over 20, 20–49, 50–69 and over 70 years) for the APC estimation of age-adjusted mortality rates. Overall, significant declines per year in the age-adjusted mortality rates were demonstrated for the entire sample (over 20 years) across the 18-year period studied (APC: –5.59%; 95% CI: –8.5 to –2.5% for males; *p*-value < 0.05 and APC: –7.02%; 95% CI: –11.2 to –2.8% for females; *p*-value < 0.05); no significant difference was found between the genders (Figure 2). In an analysis performed with two Joinpoints, significant declines were observed from 1994 to 2001 (APC: –21.22%; 95% CI: –27.9 to –13.9%) and from 1994 to 2003 (APC: –12.86%; 95% CI: –22.2 to –2.5%) for men and women respectively (Figure 3). The declining trends were greatest for patients aged over 70 years old with the age-adjusted mortality rates in younger groups



**Figure 1 – Estimated crude mortality rate (per 100,000 inhabitants) according to age range and gender. Data are expressed as mean ± standard deviation (error bars). Similar values were observed for the 20- to 49-year age group, 50- to 69-year age group and over 70-year age group (Kruskal–Wallis test with Dunn's multiple comparisons test).**



**Figure 2 – Trends in age-adjusted mortality rate for over 20-year-old males and females from 1994 to 2011.**



**Figure 3 – Significant changes over successive time segments (Joinpoints) for over 20-year-old males and females from 1994 to 2011.**

**Table 1 – Estimated annual percent change of the age-adjusted mortality rates of patients with myeloid leukemia according to age range and gender in the Vale do Paraíba from 1994 to 2011.**

Age range (years)	Male	Female
Over 20	-5.59 (-8.5 to -2.5) <sup>a</sup>	-7.02 (-11.2 to -2.8) <sup>a</sup>
20-49	-2.40 (-5.8 to 1.1)	-3.60 (-7.3 to 0.1)
50-69	-3.90 (-7.2 to -0.5) <sup>a</sup>	-0.30 (-3.7 to 3.3)
Over 70	-6.52 (-10.3 to -2.6) <sup>a</sup>	-8.01 (-13.2 to -2.5) <sup>a</sup>

Data are expressed as mean rate of change (%) and (95% confidence interval).

<sup>a</sup> p-value < 0.05.

**Table 2 – Estimated annual percent change of the age-adjusted mortality rates of patients with myeloid leukemia according to age range in Brazil from 1994 to 2011.**

Age range (years)	Mean annual percent change	95% confidence interval
Over 20	+1.4 <sup>a</sup>	+0.6 to +2.2
20-49	-1.2 <sup>a</sup>	-1.9 to -0.6
50-69	+0.3	-0.4 to +1.0
Over 70	+2.3 <sup>a</sup>	+1.4 to +3.1

<sup>a</sup> p-value < 0.05.

declining albeit not significantly except for males aged 50-69 years old (Table 1). With regard to Brazil as a whole, a significant upward trend was observed for both the entire sample (over 20 years) and for patients aged over 70 years. There was a significant decline for patients aged 20-49 years and an insignificant increase for patients aged 50-69 years (Table 2).

## Discussion

SUS is available to all Brazilian citizens although roughly 25% of the population has private health insurance<sup>7</sup>; we therefore believe that data extrapolated from the DATASUS database are useful for clinical and epidemiological studies. However, an important limitation of this study regards the quality of data. Registration of erroneous ICD codes results in misclassification and could be responsible for differences in mortality rates observed in this series. It should also be stressed that, in many areas, access to timely cancer care is impaired by the inadequate infrastructure of the healthcare system, especially in low-income and geographically isolated populations with these cases being more likely to remain unreported than cases treated in hospitals. In addition, deaths from patients with either acute or chronic myeloid leukemia are registered in the DATASUS database as myeloid leukemia which is unsatisfactory because mortality rates vary between acute and chronic myeloid leukemia. This complicates comparisons and in particular makes it difficult to interpret regional differences. Furthermore, the study was based on a cross-sectional structure and registries did not state whether deaths occurred during or after specific treatments, therefore a cause-effect relationship could not be established. Thus, an exploratory and comparative analysis was done to report the mortality

rates and the results gained over a period of time in the Vale do Paraíba.

The diagnosis of AML may explain, at least in part, the increased crude mortality rates observed in the elderly group. AML presents at all ages, but its incidence increases with age and outcomes are strongly age and performance status dependent. Older patients have more comorbidities and a higher incidence of poor prognostic factors, such as secondary leukemia and high-risk cytogenetics. Moreover, early death rates of 15% to 55% have been reported among the elderly and even in cases of APL, a lower survival rate has been described in older patients.<sup>8,9</sup>

Overall, our series suggests that mortality dropped significantly over the years in this region. The possible reasons for this finding are based on the improvements in the quality of care which was introduced by our team in the Vale do Paraíba since early 1999; the practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer, hospital environmental precautions, more intensive chemotherapy followed by autologous hematopoietic stem cell transplantation (which has been used in this region since 2004) and allogeneic bone marrow transplant from related or unrelated donors probably led to better survival of these patients. Besides, new treatment options such as the use of all-trans retinoic acid (ATRA) plus chemotherapy, which was associated with a high complete remission rate in newly diagnosed APL, and the use of anti-tyrosine kinase targeted therapy specific for the BCR-ABL rearrangement in CML (authorized in Brazil since October, 2001) could also explain the observed decrease in mortality. On the other hand, our findings contrast with the upward trend in mortality seen in Brazil as a whole. We believe that different Brazilian regions also have experienced improvements however, there is still a biased allocation of resources, underinvestment in equipment and infrastructure and inequities in cancer care across population groups; some institutions provide all aspects of health care to specific populations while others are excluded which consequently reflects on the mortality rates observed in Brazil.

The age-adjusted mortality rates in younger groups declined insignificantly over the last few years. Furthermore, a striking finding of the present study is that the decrease was the greatest for over 70-year-old patients contrasting with those observed for the same age group in Brazil. This scenario is difficult to explain. It has been demonstrated that patients who were diagnosed with AML at younger ages have higher survival rates,<sup>10</sup> and CML is expected in this age range. Based on these reasons and considering the aforementioned improvements in the quality of care in this region, we expected to find a more significant drop across time in the younger groups. It is possible that a significant decline could not be demonstrated for younger patients because death rates were consistently low over the years. Moreover, in another study regarding demographic characteristics of hematological malignancies in the Vale do Paraíba,<sup>11</sup> it was demonstrated that the period between the first symptoms and definitive diagnosis of the disease in this age range was greater than two months in 65% of the cases; a delay in receiving a proper diagnosis which consequently worsens the chances of successful chemotherapy may explain these findings. With regard to older patients, improvements in early death rates and long

term survival were demonstrated even in older patients with AML<sup>9</sup>; the fall in mortality rates with advancing age points to an increase in the quality of care, suggesting that old patients may be receiving optimal treatment for their conditions in this region.

Finally, the drop in cancer mortality is not surprising. The American Cancer Society recently demonstrated that cancer death rates have declined 20% over the last 20 years in the United States.<sup>2</sup> In addition, authors have reported an association between socioeconomic status and mortality due to cancer in different regions of the world.<sup>12-15</sup> In this context, the Vale do Paraíba has made great strides due to the economic and social development of the population, including territorial expansion and industrialization. The present work suggests that our combined and continuous efforts to make better and sustained improvements in the quality of cancer care contributed to the decrease in myeloid leukemia mortality rates across the 18-year period studied.

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## Conclusion

Despite the methodological limitations, the data of this study suggest a significant decline in age-adjusted mortality rates of patients diagnosed with myeloid leukemia from 1994 to 2011 in the Vale do Paraíba, State of São Paulo.

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## Conflicts of interest

The authors declare no conflicts of interest.

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