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Original Article

# Demographic and Clinical Characteristics of Chronic Myeloid Leukemia Patients: A Study on Confined Populations of Southern India

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## Abstract

**Context:** Chronic myeloid leukemia (CML) is one of the most common hematological malignancies in all populations throughout the world. Even though the pathophysiology of CML was well explained in majority of the studies, the incidence of CML was shown to exhibit population diversity, and hence, the demographic factors underlying CML origin remain to be understood. Further, the introduction of tyrosine kinase inhibitors had revolutionized the treatment of CML over the years; however, there is a need for developing tailoring therapy to individual risk since the patient clinical heterogeneity poses a major problem during drug response. Therefore, the study of basic clinical picture may aid in planning treatment strategies for CML patients. **Aim:** The aim of this article is to study the epidemiological and clinical variables associated with the prognosis of CML. **Subjects and Methods:** We have considered the distribution of various demographic and clinical variables among 476 CML patients diagnosed at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. **Statistical Analysis Used:** All the analyses were performed through SPSS software (version 21.0). Correlation and Cox regression analyses were also performed. **Results:** Apart from the elevated male sex ratio in CML incidence, high frequency of males was observed to be nonresponders to imatinib mesylate (IM). IM response was shown to be dependent on phase of diagnosis, whereas overall survival of CML patients depends on the age at onset and response to IM. **Conclusions:** The study of epidemiology and clinical picture of CML patients may help in planning better treatment strategies at diagnosis to achieve long-term progression-free survival.

**Keywords:** *Chronic myeloid leukemia, clinical variable, epidemiology, imatinib mesylate, survival*

## Introduction

Chronic myeloid leukemia (CML) is one of the most commonly diagnosed hematological malignancies among adults worldwide, exhibiting population diversity in incidence among Asian and other populations, and even between subpopulations. In spite of extensive knowledge generated on the molecular basis of CML, the etiopathogenesis of 9:22 translocation still remains obscure. Various epidemiological studies on CML have indicated the role of few environmental factors in conferring increased risk to CML, which was further shown to depend on the genetic susceptibility of individuals and level of environmental interactions. Hence, understanding the etiology of CML is considered very important in elucidating the factors influencing CML origin. At present, major sources available for the information on epidemiology of CML are Mortality Statistics, European Cancer Registries (Swedish Cancer Registry and Saarland Registry in Germany), and Database of Surveillance Epidemiology and End Results program of the United States from National Cancer Institute.[1]

Since the introduction of targeted drugs in 2001, relative survival of CML patients had been shown to increase and mortality rates were found to decrease by the use of tyrosine kinase inhibitors (TKIs).[2,3] The 5-year survival rate of CML patients had been shown to be doubled over the past two decades after the discovery of TKIs, from 31% in the early 1990s to 63% for patients diagnosed from 2005 to 2011.[4] About 90% of CML patients were reported to be diagnosed in the initial, less severe chronic phase (CP). However, 60%–80% of the patients reported in the final, acute blast crisis (BC) phase were



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found to be preceded by the intermediate accelerated phase (AP),[5] indicating that phase at diagnosis plays a major role in CML prognosis. Majority of the CML patients are given imatinib mesylate (IM) as the front-line therapy, irrespective of the phase in which they are diagnosed, and IM response is measured at hematological, cytogenetic, and molecular levels based on the differential blood cell counts, cytogenetic analysis, and polymerase chain reaction (PCR) tests, respectively, to monitor the progression of disease on a regular basis. The study of the patient clinical picture is probably one of the better approaches to assessing the progression of CML and overall response to IM.

## Subjects and Methods

### Study population

Population recruited for the study consisted of CML cases ($n$ = 476) from different socioeconomic strata (from the states Telangana and Andhra Pradesh) diagnosed at Nizam's Institute of Medical Sciences, Hyderabad, India (during the period 2004–2012). Epidemiology information was obtained from the patient through a prescribed questionnaire. Only primary Philadelphia chromosome positive CML cases on IM treatment were included, irrespective of the phase of disease and duration of treatment being given to the patient. None of these cases were on any other clinical trials. Complete clinical information of the patient, including follow-up and treatment modalities, was noted from the tumor registry of the hospital with the help of a medical oncologist. In spite of our sincere attempts to follow-up all the recruited cases, few patients failed to report regularly and were lost to follow-up due to unknown reasons, and hence, their information could not be recorded. For the case–control comparison study, 449 age- and sex-matched healthy controls without family history of cancers were recruited from local population by visiting households, offices, blood donation camps, etc. Informed consent was taken from all the subjects included in the study. Patient's personal information was not revealed in the data.

### Statistical analyses

The baseline clinical characteristics of CML patients such as differential cell count, platelet count, percentage of blasts, and spleen size were considered in calculating Sokal, Hasford, and European Treatment and Outcome Study (EUTOS) risk scores,[6-8] using the online calculator,[9] which helped in estimating the risk of progression of patients at the time of diagnosis by grouping them into low-, intermediate-, and high-risk groups. In general, patients in the low-risk groups are expected to achieve complete cytogenetic response (CCR) to treatment earlier than those in the high-risk group.

Bivariate Pearson's correlation coefficient test was performed to analyze the strength of relationship between two clinical variables. Cox regression analysis was done to identify the impact of clinical characteristics on the event-free survival (EFS) rate. EFS rate was calculated for CML patients diagnosed in CP, as the duration in months, from the date of initiation of IM to the date of showing any sign of progression. All statistical analyses were performed using the SPSS (version 21.0, IBM, Armonk, New York, US) software.

## Results and Discussion

### Sex ratio

Even though elevated male frequency among CML cases is the universal observation, the male-to-female ratio (sex ratio) was reported to vary between different geographic areas, also for different countries of the Asian population.[10] In India, CML incidence rates were reported as 0.8–2.2 in males and 0.6–1.6 in females (National Cancer Registry Program, 2005),[11] with a wide variation in sex ratio ranging from 1:0.8 to 3:1 for different areas,[12] indicating male predominance. Our study also revealed elevation in male sex frequency similar to the earlier reports with a sex ratio of 1.88:1 [Table 1]. The male preponderance might be attributed to their genetic constitution, inherent immune differences, hormonal levels, likelihood of occupational exposure to various types of radiation and chemicals, and diet, smoking, and alcoholic habits.[13]

**Table 1: Demographic characteristics of chronic myeloid leukemia cases and controls**

| Characteristic | Controls[@], *n* (%) | CML cases, *n* (%) | Mean age at onset±SD | Sex ratio |
|---|---|---|---|---|
| Age at onset (years)[£] | | | | |
| <20 | 62 (13.8) | 35 (7.4) | 15.00±3.73 | 1.92:1 |
| 20-40 | 269 (59.9) | 280 (58.8) | 30.74±6.10 | 1.64:1 |
| >40 | 118 (26.3) | 161 (33.8) | 50.73±7.50 | 2.43:1 |
| Gender | | | | |
| Male | 293 (65.3) | 311 (65.3) | 36.84±13.05 | 1.88:1 |
| Female | 156 (34.7) | 165 (34.7) | 35.41±12.32 | |
| Living area | | | | |
| Rural | 200 (47.3) | 303 (65.2) | 35.49±12.27 | 2.00:1 |
| Urban | 223 (52.7) | 162 (34.80) | 38.35±13.38 | 1.61:1 |
| Occupation | | | | |
| Agricultural laborers | 15 (3.6) | 120 (25.4) | 38.88±11.56 | 2.64:1 |
| Laborers | 110 (26.1) | 160 (33.9) | 36.94±11.00 | 2.90:1 |
| Others | 297 (70.4) | 192 (40.7) | 34.26±14.56 | 1.11:1 |
| Diet | | | | |
| Veg | 79 (18.6) | 31 (7.5) | 41.48±14.26 | 1.58:1 |
| Nonveg | 346 (81.4) | 385 (92.5) | 36.13±12.56 | 1.89:1 |
| Habits | | | | |
| Smokers, alcoholics | 72 (17.8) | 112 (28.8) | 41.08±11.34 | - |
| No habits | 332 (82.2) | 277 (71.2) | 34.17±12.51 | - |

[£]CML cases: mean age=36.34±12.80; range=7-80; median=35; mode=45, [@]age and sex matched controls were included in the study. CML – Chronic myeloid leukemia; SD – Standard deviation

## Age distribution

Lower age at onset was observed mostly for Asian countries ranging from 38 to 40 years as compared to the Western population.[10] The mean age at onset of CML patients (36.34 years) (standard deviation: 12.8) observed in the present study showed a similar trend with that of the Asian populations with a range of 7–80 years and median age of 35 years. Lower mean age at onset could be attributed to high prevalence of chronic infections or shorter life expectancy of elderly people after diagnosis.[14] However, in our study, CML was found to be highly prevalent in the age groups of 20–40 years (58.8% with mean age 30.74 ± 6.10) and >40 years (33.8% with mean age 50.73 ± 7.50) [Table 1], confirming that mostly middle-aged people had higher risk to develop CML. With respect to sex, males belonging to the age group >40 years were found to be more frequently affected than females in the same age group (sex ratio 2.43:1).

## Environmental factors in conferring risk to chronic myeloid leukemia

Previously, exposure to ionizing radiation was considered as the only risk factor for CML which was evident from increased CML incidence among the survivors of atomic bomb detonations in Hiroshima and Nagasaki[15] and also among the workers of Chernobyl nuclear power plant accident.[1] Electromagnetic field was also considered as one of the risk factors for CML in few reports.[16,17] Few studies implied various chemicals including pesticides in contributing to a little or moderate risk to CML development.[1] In our study, there were no data on kind and level of exposure to various environmental factors. However, area of living and occupation were considered to evaluate the environmental risk confounding factors in CML development.

### *Area of living*

Higher frequency of patients belonged to rural areas (65.2%) than those residing in the urban regions (34.8%) [Table 1]. This might be attributed to the possible occupational exposure of the people in rural areas to various chemicals including pesticides as most of them were observed to be agricultural laborers. Among CML patients from rural area, the frequency of male patients was found to be twice that of females (sex ratio 2.00:1), indicating sensitivity of males to environmental factors.

### *Occupation*

Frequency of agricultural laborers was found to be highly elevated in CML group (25.4%) when compared to that of control population (3.6%). Vojdani *et al*. reported that pesticide exposure affected the functioning of the blood vascular system,[18] and improper use of pesticides was shown to induce neurological and hematological complications in individuals,[19,20] which might be the reason for enhanced risk of CML development among agriculture laborers. The sex ratio was also found to be elevated among agricultural laborers and other laborers (working in factories, house construction, and other fields) (2.64:1 and 2.90:1, respectively) [Table 1], indicating that males exposed to pollutants may be at more risk for CML development compared to females.

## Personal history of chronic myeloid leukemia patients

### *Diet*

In the present study [Table 1], the frequency of vegetarians was found to be almost half (7.5%) in CML cases as compared to that of controls (18.6%). Further, higher mean age at onset of CML patients who were on vegetarian diet (41.48 ± 14.26 years) when compared to that of nonvegetarian CML patients (36.13 ± 12.56 years) confirmed the protective role of vegetarian diet reported by earlier studies.[21]

### *Smoking and/or alcoholic history*

In our study, the frequency of males with smoking and alcoholic history was found to be elevated in CML group (28.8%) when compared to that of controls (17.8%) [Table 1]. Among the cases with this history, 14.4%, 5.76%, and 12.38% were found to be smokers, alcoholics, and both smokers and alcoholics, respectively, indicating that smoking alone or in combination with alcohol consumption might have confounded the risk for CML. These results were supported by the findings of Kabat *et al*.[22] and Musselman *et al*.[23]

## Sokal, Hasford, and European Treatment and Outcome Study risk scores

Majority of the CML patients were in the high- and intermediate-risk groups of Sokal and Hasford scores (46.1% and 53.0%, respectively) [Table 2]. However, the frequency of patients was found to be reduced for EUTOS high-risk group (39.2%), for which scoring was based only on the basophil count and spleen size. Sex ratio was also elevated for the high-risk group of Hasford score (2.09:1), which was similar to the report of Berger *et al*.,[24] where female patients were found to be more frequent in the low-risk groups of Sokal score.

## Phase of chronic myeloid leukemia

In the present study, 85.5% of the patients were found to be diagnosed in CP [Table 2], and 7.8% and 6.7% of patients were diagnosed in AP and BC, respectively. The sex ratio was highly elevated for the patients in BC (2.88:1), indicating that males were found to be more frequent in progression compared to females at the time of diagnosis.

## Imatinib mesylate response

In general, 95% and 80% of the patients in early CP-CML were shown to achieve complete hematological response (CHR) and CCR, respectively, and these responses were found to be stable in most patients with

**Table 2: Distribution of clinical characteristics of chronic myeloid leukemia patients**

| Clinical variable | *n* (%) | Mean age±SD | Sex ratio |
|---|---|---|---|
| Phase of CML (*n*=463) | | | |
| Chronic | 396 (85.5) | 36.61±12.863 | 1.87:1 |
| Accelerated | 36 (7.8) | 35.03±13.018 | 1.77:1 |
| Blast-Crisis | 31 (6.7) | 35.19±11.429 | 2.88:1 |
| Hematologic response (*n*=341) | | | |
| Complete | 224 (65.7) | 35.93±12.150 | 1.60:1 |
| Partial | 53 (15.5) | 35.89±12.250 | 2.31:1 |
| No response | 64 (18.8) | 38.98±13.368 | 2.37:1 |
| Cytogenetic response (*n*=326) | | | |
| Complete | 195 (59.8) | 34.87±12.580 | 1.75:1 |
| Partial | 59 (18.1) | 33.97±11.269 | 2.69:1 |
| No response | 72 (22.1) | 38.08±11.734 | 1.77:1 |
| Molecular response (*n*=381) | | | |
| Responders | 213 (55.9) | 35.23±12.527 | 1.63:1 |
| Nonresponders | 168 (44.1) | 35.92±12.341 | 2.17:1 |
| Sokal score (*n*=332) | | | |
| Low risk | 59 (17.8) | 29.31±10.729 | 1.95:1 |
| Intermediate risk | 120 (36.1) | 36.74±12.469 | 1.67:1 |
| High risk | 153 (46.1) | 38.57±13.048 | 1.64:1 |
| Hasford score (*n*=270) | | | |
| Low risk | 59 (21.9) | 33.69±8.655 | 1.57:1 |
| Intermediate risk | 143 (53.0) | 34.27±11.622 | 1.42:1 |
| High risk | 68 (25.2) | 42.03±14.575 | 2.09:1 |
| EUTOS score (*n*=355) | | | |
| Low risk | 216 (60.8) | 36.90±12.825 | 2.04:1 |
| High risk | 139 (39.2) | 36.03±12.410 | 1.44:1 |

CML – Chronic myeloid leukemia; SD – Standard deviation; EUTOS – European Treatment and Outcome Study

a risk of relapse of 4%–6%/year.[25] For patients with advanced CML (AP or BC), achievement of CHR and major (complete and partial) cytogenetic response were shown to occur only in 25%–37% and 10%–30% of the patients, respectively.[10] In the present study, 65.7% of the CML patients were shown to achieve CHR. Nearly 1/3$^{rd}$ frequency of patients did not achieve HR (partial: 15.5% and poor: 18.8% of the patients) in time. CCR was observed in 59.8% of the CML cases, while 55.9% cases showed complete molecular response (CMR)/major molecular response which included the patients diagnosed or reported in all three phases of CML. The sex ratio was found to be highly elevated among poor responders with respect to all three types of responses monitored [Table 2], indicating the reduced response of male patients to treatment.

### *Phase versus imatinib mesylate response*

About 72.1%, 65.23%, and 58.43% of the patients diagnosed in the CP were found to achieve CHR, CCR, and CMR, respectively, whereas only very few patients diagnosed in BC showed good responses. The frequency of patients diagnosed in AP with good drug response was also low when compared to patients in CP but higher when compared to those of BC [Table 3]. The results of the present study were found to be in accordance with the earlier studies by Kumar.[25]

**Table 3: Imatinib mesylate response with respect to the phase of chronic myeloid leukemia**

| Category of response | Chronic phase | Accelerated phase | Blast crisis |
|---|---|---|---|
| Hematologic response (%) | | | |
| Complete | 211 (72.01) | 8 (38.10) | 5 (19.23) |
| Partial | 48 (16.38) | 3 (14.29) | 1 (3.85) |
| No response | 34 (11.60) | 10 (47.62) | 20 (76.92) |
| Cytogenetic response (%) | | | |
| Complete | 182 (65.23) | 10 (47.62) | 3 (11.54) |
| Partial | 54 (19.35) | 1 (4.76) | 4 (15.38) |
| No response | 43 (15.415) | 10 (47.62) | 19 (73.08) |
| Molecular response (%) | | | |
| Responders | 194 (58.43) | 10 (47.62) | 4 (19.05) |
| Nonresponders | 138 (41.57) | 11 (52.38) | 17 (80.95) |

### Overall survival

In general, 90% of the people in CP were reported to live for 5 years or beyond, whereas patients were found to be alive for only 3–6 months rather than years if diagnosed in or progressed to BC.[26] In our study, no significant elevation in the sex ratio was found for the patients showing primary resistance (not able to achieve CCR within 6–12 months after the start of treatment), for the patients showing secondary resistance to IM (initial response to IM and later showing relapse), and for the relative 4-year overall survival of the patients. However, the mortality rate of patients as per the hospital records was found to be higher for the male population compared to the female population (4.02:1) [Table 4].

### Correlation between clinical variables

Results of the test [Table 5] revealed that a negative correlation was observed between age at onset and white blood cell count/platelet count/EFS. Many reports indicated reduced response rates among the older patients,[27,28] which might be one of the reasons for the faster progression of disease and reduced EFS rates among elderly patients than younger patients. All risk scores were found to be in positive correlation with each other. Importantly, EUTOS score showed a highly significant negative correlation with the relative 4-year overall survival rate of the CML patients. Further, the EFS rates showed a significant positive correlation with the relative 4-year overall survival rates.

### Cox regression analysis

In the present study, the analysis was done for 209 CML patients diagnosed in CP for whom the data on EFS rate were available [Table 6]. Sex of the patient was not found to have any effect on the EFS rate. However, the patients with early age at onset (<20 years) were found to have reduced risk for progression and increased EFS rate with borderline

significance when compared to middle-aged (20–40 years) patients, similar to the results of correlation analysis. The Sokal, Hasford, and EUTOS risk scores were not observed to influence the EFS rate of CML patients. This might suggest the independence of CML progression on the baseline clinical characteristics of the patients. Nevertheless, a new score calculated from higher age and higher percentage of peripheral blasts, enlarged spleen, and low platelet count was shown to be significantly associated with increased probability of death of CML patients and was proven to be a better scoring system for predicting the long-term prognosis of CML patients compared to other scores.[29]

When the IM response was considered, patients who had not achieved HR had 2.10-fold increased risk for progression and shortened EFS rate. Further, cytogenetic partial and poor responders had significantly elevated risk for progression which suggests strong dependence of CML progression on IM response [Table 6]. Molecular response

**Table 4: Survival rates of chronic myeloid leukemia patients and gender distribution**

| Survival rates | Males, *n* (%) | Females, *n* (%) | Sex ratio |
|---|---|---|---|
| EFS | | | |
| Primary resistance | 47 (46.08) | 24 (52.17) | 0.88:1 |
| Secondary resistance | 55 (53.92) | 22 (47.83) | 1.13:1 |
| Overall survival (years) | | | |
| ≤4 | 117 (44.15) | 75 (53.57) | 0.82:1 |
| >4 | 148 (55.84) | 65 (46.43) | 1.20:1 |
| Event | | | |
| Alive | 242 (91.32) | 136 (97.84) | 0.93:1 |
| Dead | 23 (8.68) | 3 (2.16) | 4.02:1 |

EFS – Event-free survival

**Table 5: Correlation between the clinical variables among chronic myeloid leukemia cases**

| Correlation coefficient (*r*)\significance (*P*) | Age at onset | WBC count | Platelet count | Sokal score | Hasford score | EUTOS score | EFS | Overall survival |
|---|---|---|---|---|---|---|---|---|
| Age at onset | | −0.132** | −0.110* | 0.113* | 0.235** | −0.040 | −0.140* | −0.093 |
| WBC count | 0.006 | | 0.084 | 0.111* | 0.136* | 0.207* | −0.060 | −0.031 |
| Platelet count | 0.024 | 0.085 | | 0.009 | 0.044 | −0.079 | 0.139 | 0.093 |
| Sokal score | 0.041 | 0.045 | 0.870 | | 0.683** | 0.359** | −0.081 | 0.082 |
| Hasford score | 0.000 | 0.026 | 0.479 | 0.000 | | 0.548** | 0.026 | −0.129 |
| EUTOS score | 0.448 | 0.000 | 0.145 | 0.000 | 0.000 | | −0.041 | −0.195** |
| EFS | 0.043 | 0.403 | 0.057 | 0.346 | 0.784 | 0.610 | | 0.538** |
| Overall survival | 0.107 | 0.604 | 0.127 | 0.256 | 0.113 | 0.004 | 0.000 | |

*r*=Pearson correlation coefficient; *P*=Significance *<0.05, **<0.01. WBC – White blood cell; EUTOS – European Treatment and Outcome Study; EFS – Event-free survival

**Table 6: Cox regression analysis of clinical characteristics on event-free survival rate in chronic phase - chronic myeloid leukemia**

| Variable | Categories | Hazardous risk | 95% CI | *P* |
|---|---|---|---|---|
| Age at onset | 20-40 years (*n*=125) | 1.00 (reference) | - | - |
| | <20 years (*n*=17) | 0.58 | 0.32-1.03 | 0.06# |
| | >40 years (*n*=67) | 1.22 | 0.89-1.68 | 0.21 |
| Sex of patient | Males versus females | 1.17 | 0.85-1.60 | 0.34 |
| Sokal score | Low risk (*n*=25) | 1.00 (reference) | - | - |
| | Intermediate (*n*=54) | 0.80 | 0.48-1.33 | 0.38 |
| | High risk (*n*=62) | 1.06 | 0.63-1.76 | 0.83 |
| Hasford score | Low risk (*n*=22) | 1.00 (reference) | - | - |
| | Intermediate (*n*=65) | 1.15 | 0.70-1.90 | 0.59 |
| | High risk (*n*=26) | 0.87 | 0.46-1.63 | 0.65 |
| EUTOS score | Low risk (*n*=100) | 1.00 (reference) | - | - |
| | High risk (*n*=61) | 0.99 | 0.70-1.39 | 0.94 |
| Hematologic response | Complete (*n*=88) | 1.00 (reference) | - | - |
| | Partial (*n*=40) | 1.05 | 0.71-1.55 | 0.81 |
| | No response (*n*=48) | 2.10 | 1.37-3.23 | 0.001** |
| Cytogenetic response | Complete (*n*=78) | 1.00 (reference) | - | - |
| | Partial (*n*=38) | 1.49 | 1.00-2.23 | 0.05# |
| | No response (*n*=55) | 1.42 | 0.96-2.12 | 0.08# |
| Molecular response | Complete/major (*n*=40) | 1.00 (reference) | - | - |
| | No response (*n*=152) | 1.09 | 0.75-1.57 | 0.65 |

#*P* significant at 0.10; **P* significant at 0.05; ***P* significant at 0.01. CI – Confidence interval; EUTOS – European Treatment and Outcome Study

did not seem to have effect on the progression and EFS rate of CP-CML patients. Molecular response is based on the presence of BCR-ABL fusion gene, and majority of the patients were found to be with minimal residual disease containing detectable levels of BCR-ABL fusion gene on real-time PCR. These patients may not be showing any event of progression or death until and unless the BCR-ABL levels rise.

## Conclusions

The association of male sex with occupation and area of living as observed in the present study strongly suggests the effect of interaction of environmental factors and inherent genetic susceptibility for the enhanced risk to CML development among males. In addition, elevated frequency of males with advanced phase of CML, high-risk scores, and poor-drug response observed in the present study also imply the genetic susceptibility of males for the enhanced risk of CML progression. Furthermore, the observation supported the earlier reports which found that the drug response of patients depend on their age at onset and phase of diagnosis, and the progression of disease in turn depends on the response to TKIs. Hence, treatment strategies may be planned by considering these factors for achieving better prognosis and long-term disease-free or overall survival among CML patients.

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### Conflicts of interest

There are no conflicts of interest.

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