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Smoking, Occupational Exposure, Geographic Distribution, and Familial Cancer History in Relation to Disease Burden and Cardiac Outcomes in Chronic Myeloid Leukemia: A Cross-Sectional Study

Iman Ahmed Kassem[1], Hanan A. Hegazy[2], Ahmed Akef[3], Reda Ataarabeh Elberry[4], Adel M. Abdou[5], Sherif A. Mohamed[6], Ahmed Abd Elmoez Ali Saad[5], Mohammad Abd Elhameed Alwaseef[5], AbdElsalam Fathy AbdElsalam Mohammad[5], Hassan Babiker Mohamed Lazim[7], Yasir Osamah Abushuaylan[8], Mahmoud Radwan Khalifa[9], Abdulmabod Omar[5], Alshaimaa H. Abd Elmaksoud[3]

[1] Department of Clinical Pathology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt.
[2] Environmental and Occupational Medicine Department, National Research Centre, Giza, Egypt.
[3] Department of Clinical Pathology, Faculty of Medicine, Mansoura University, Mansoura, Egypt.
[4] Department of Public Health, Community and Occupational Medicine, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.
[5] Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
[6] Department of Medical Biochemistry, Faculty of Medicine, Al-Azhar University, Assiut, Egypt.
[7] Department of Medical Education, College of Medicine, Najran University, Najran, Saudi Arabia.
[8] Laboratory Department, Ministry of National Guard-Health Affairs, Jeddah, Saudi Arabia.
[9] Cardiology Department, National Heart Institute, Cairo, Egypt.
Corresponding author: Mohammad Abd Elhameed Alwaseef, Department of Clinical Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.

ABSTRACT:

Background & Aim: Chronic myeloid leukemia (CML) shows variable hematologic burden and cardiac complications. This study evaluated smoking and occupational exposure (modifiable), and geographic distribution and familial cancer history (non-modifiable), as predictors of disease burden and cardiac outcomes in patients with CML.

Methods: A retrospective cross-sectional study was conducted among 110 patients with confirmed chronic myeloid leukemia (CML) across participating centers from January 2025 to December 2025. Disease burden was assessed using hematologic indices, blast percentages, splenic size, and clinical severity indicators. Cardiac outcomes were assessed

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by transthoracic echocardiography according to a prespecified composite definition that included reduced ejection fraction, diastolic dysfunction, pulmonary hypertension, significant valvular regurgitation, or left atrial/ventricular structural abnormality. Associations were evaluated using chi-square tests, independent-samples t-tests, one-way ANOVA, correlation analysis, and multivariable regression models as appropriate.

Results: Cardiac dysfunction according to the prespecified composite definition was identified in 82 of 110 patients (74.5%). Mean EF was 63.1 ± 4.5%, and only one patient (0.9%) met the reduced-EF criterion. Grade 1–2 diastolic dysfunction was the most frequent echocardiographic abnormality (46.4%), followed by significant valvular regurgitation (24.5%) and pulmonary hypertension (9.1%). On bivariate analysis, cardiac dysfunction differed significantly across occupational exposure categories ($P = 0.030$), whereas no significant associations were observed with smoking, geographic residence, familial cancer history, or sex. Patients with cardiac dysfunction were significantly older than those without cardiac dysfunction (52.8 ± 14.0 vs. 29.8 ± 8.2 years, $P < 0.001$). In multivariable logistic regression, age was independently associated with the composite cardiac outcome (OR = 1.19, 95% CI: 1.11–1.27, $P < 0.001$), while occupational exposure was not independently significant.

Conclusion: In this cohort of patients with CML, age was the strongest independent factor associated with the prespecified composite cardiac outcome. Although occupational exposure was associated with cardiac dysfunction on bivariate analysis, this association was attenuated after adjustment for other covariates. The high prevalence of the composite outcome was predominantly attributable to diastolic and other echocardiographic abnormalities rather than reduced EF. Prospective studies incorporating detailed treatment exposure, cardiovascular risk factors, and longitudinal echocardiographic assessment are needed to clarify the clinical significance of these findings.

1. INTRODUCTION

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm driven by the BCR-ABL1 fusion gene, characterized by uncontrolled granulocytic proliferation, leukocytosis, and splenomegaly [1]. Disease burden in CML is conventionally captured through hematologic indices-total leukocyte count (TLC), peripheral and bone marrow blast percentage, hemoglobin level, and splenic size-which together reflect tumor mass and clinical severity at presentation, and which frequently guide decisions on treatment intensity and monitoring frequency [2].

Cardiac involvement is increasingly recognized in CML, arising from both disease-intrinsic mechanisms and treatment effects. Tyrosine kinase inhibitors (TKIs), the cornerstone of modern CML therapy, have been repeatedly linked to vascular and cardiac adverse events, including hypertension, arrhythmia, and heart failure [3]. However, the intrinsic burden of untreated or newly diagnosed disease-anemia, a hypermetabolic state, leukostasis, and chronic low-grade inflammation-can independently strain the myocardium, manifesting as diastolic dysfunction, reduced ejection fraction, or pulmonary hypertension even before TKI exposure begins [4,5]. Distinguishing disease-intrinsic cardiac strain from treatment-related toxicity therefore remains an important, unresolved question in cardio-oncology.

Smoking is a well-established driver of oxidative stress, endothelial dysfunction, and microvascular injury, mechanisms that plausibly worsen both clonal hematologic progression and cardiovascular resilience [6]. Occupational exposures-pesticides and agrochemicals among farmers, industrial solvents and particulates among manual workers, and traffic-related pollutants among drivers-have similarly been implicated as dual threats, contributing to leukemogenesis while promoting endothelial and myocardial injury through chronic low-grade toxin exposure [7].

Also, non-modifiable epidemiologic factors can influence the way disease manifests. Differential exposures to the environment (urban versus semi-urban/rural), access to health care, and diagnostic delay may be reflected by geographic residence, and a positive family history of cancer might represent a shared genetic or environmental susceptibility [8]. Although there has been

an increasing interest in cardio-oncology and combined data on these modifiable and non-modifiable predictors and their relationship to both the burden of hematologic disease and echocardiographic cardiac outcomes in CML is growing, little data have been integrated to examine relationships between them, especially in North African/Middle Eastern populations where occupational and environmental exposure profiles differ significantly from previously studied Western cohorts.

The ability to identify those of these predictors that are predominantly related to the hematologic tumor burden, those that are closely related to the myocardium, and those that are confounded by age or disease chronicity is key to defining the cardiac surveillance pathway for individual patients rather than treating everyone the same.

Accordingly, this study was designed to assess the smoking status, occupational exposure category, geographic distribution, and familial cancer history as predictors of disease burden and cardiac dysfunction in a well-defined bivariate and multivariable statistical model, which were pre-specified and adjusted for age and sex of the studied Egyptian CML patients.

2. METHODS

2.1 Study Design and Setting

This retrospective observational cross-sectional analytical study was conducted using hematology and internal medicine records from tertiary and secondary healthcare centers covering the period January 2025 to December 2025. The study complied with the ethical principles of the Declaration of Helsinki [9]. Institutional review board approval was obtained prior to data extraction form faculty of medicine, Al-Azhar University, Egypt, and only retrospective, anonymized data were analyzed with no direct patient contact or intervention. The study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cross-sectional studies [10].

2.2 Study Population

The final analytic sample comprised 110 patients with a confirmed diagnosis of CML based on clinical, hematological, and laboratory criteria. Inclusion criteria were age ≥18 years with Comprehensive geriatric assessment is done for all cases 60 years and above, complete hematological and echocardiographic data, and documented smoking status, occupation, geographic origin, and family history. Patients with missing key variables, coexisting malignancies, acute infectious or inflammatory conditions affecting leukocyte counts, or pre-existing structural heart disease unrelated to CML were excluded.

2.3 Data Collection

Information was retrieved from electronic and paper-based documents and placed into four domains. Demographic and epidemiologic data included age, sex, and geographic origin (urban: Cairo, Giza, Alexandria, and semi-urban/rural: all other governorates: Fayoum, Monofya, Sharqya, Qalyubia, Sinai, Ismailia, Menya, Beni Suef, Gharbia, Suez). For bivariate and regression analyses, current and ex-smokers were grouped as "smoker" and compared to non-smokers due to the limited number of ex-smokers. Presumed environmental exposure risk was used to classify occupation into high (farmers, industrial/manual workers, drivers, sanitation workers), moderate (delivery and technical workers, merchants), and low (housewives, students, office-based workers) exposure groups based on an a priori classification scheme. Familial cancer history was obtained as positive (defined as having a first- or second-degree relative with a hematologic or solid malignancy) or negative. Comprehensive geriatric assessment is done for all cases 60 years and above

2.4 Outcome Definitions

The primary outcome was disease burden, represented by hematologic indices, including hemoglobin level, total leukocyte count (TLC), platelet count, peripheral blood blast percentage, bone marrow blast percentage, and splenic size (cm), together with clinical severity indicators, including ICU admission at presentation and the presence of symptoms. The secondary outcome was cardiac dysfunction, defined according to the prespecified study protocol as the presence of any one of the following abnormalities on transthoracic echocardiography: EF <50% or a >10% reduction from baseline EF, grade 1–2 diastolic dysfunction, pulmonary hypertension, significant valvular regurgitation, or a left atrial or left ventricular structural abnormality.

2.5 Statistical Analysis

Data were analyzed using SPSS/R software. Continuous variables were summarized as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent-samples t-tests were used to compare

continuous variables between two groups, one-way ANOVA was used for comparisons across the three occupational-exposure categories, and chi-square tests were used to assess associations between categorical variables. Pearson or Spearman correlation analysis was performed as appropriate according to the distribution of the variables. Two multivariable regression models were used to evaluate factors associated with cardiac outcomes. Multivariable logistic regression was performed with the composite cardiac dysfunction outcome (yes/no) as the dependent variable and age, smoking status, occupational exposure category, geographic residence, familial cancer history, and sex as covariates. Multivariable linear regression was performed with EF% as the dependent variable and age, smoking status, occupational exposure category, bone marrow blast percentage, splenic size, and TLC as covariates. For categorical variables, the reference categories were non-smoking for smoking status, low occupational exposure for occupational exposure, urban residence for geographic residence, negative familial cancer history for family history, and female sex for sex. Model performance was assessed using the reported pseudo-R^2 for logistic regression and adjusted R^2 for linear regression. Multicollinearity among model covariates was assessed and was considered acceptable.

3. RESULTS

3.1 Baseline Characteristics of Participants

The cohort comprised 110 patients with a mean age of 46.9 ± 16.2 years (range 18-81 years); 58 (52.7%) were men and 52 (47.3%) were women. Geographic distribution was almost evenly split between urban (54, 49.1%; predominantly Giza and Cairo) and semi-urban/rural governorates (56, 50.9%). Occupational exposure was classified as low in 71 patients (64.5%, mostly housewives and students), high in 26 (23.6%, chiefly manual workers, farmers, and drivers), and moderate in 13 (11.8%). Twenty-two patients (20.0%) were current smokers and 7 (6.4%) were ex-smokers, together comprising 29 smokers (26.4%), while 81 (73.6%) were non-smokers. A positive familial cancer history was documented in 24 patients (21.8%), most frequently involving a parent or sibling with a solid-organ malignancy. Hepatomegaly was present in 42 patients (38.2%). Full baseline characteristics, including frequencies and percentages for all demographic and exposure variables, are shown in Table 1.

Table 1. Baseline Demographic, Epidemiologic, and Exposure Characteristics (N = 110)

Variable	n (%) or Mean ± SD
Age, years (mean ± SD)	46.9 ± 16.2 (range 18–81)
Sex	
Male	58 (52.7%)
Female	52 (47.3%)
Geographic distribution	
Urban (Cairo/Giza/Alexandria)	54 (49.1%)
Semi-urban/Rural	56 (50.9%)
Occupational exposure category	
High	26 (23.6%)
Moderate	13 (11.8%)
Low	71 (64.5%)
Smoking status	
Current smoker	22 (20.0%)
Ex-smoker	7 (6.4%)
Non-smoker	81 (73.6%)
Familial cancer history	
Positive	24 (21.8%)

Negative	86 (78.2%)
Hepatomegaly	42 (38.2%)
Hemoglobin, g/dL	9.84 ± 1.59
Total leukocyte count, $\times 10^9$/L	186.7 ± 118.9
Platelet count, $\times 10^9$/L	327.9 ± 153.8
Peripheral blood blasts, %	2.85 ± 2.33
Bone marrow blasts, %	4.10 ± 2.28
Splenic size, cm	22.5 ± 3.2
ICU admission at presentation	9 (8.2%)
symptoms	16 (14.5%)

3.2 Predictors and Disease Burden

Mean hemoglobin was 9.84 ± 1.59 g/dL, TLC 186.7 ± 118.9 $\times 10^9$/L, platelet count 327.9 ± 153.8 $\times 10^9$/L, peripheral blood blasts 2.85 ± 2.33%, bone marrow blasts 4.10 ± 2.28%, and splenic size 22.5 ± 3.2 cm. ICU admission at presentation occurred in 9 patients (8.2%) and symptoms in 16 (14.5%). Neither occupational exposure category nor smoking status was significantly associated with hematologic or tumor-burden markers in this cohort. Across occupational groups, mean TLC did not differ significantly (High 181.6 ± 111.8, Moderate 178.4 ± 110.9, Low 190.1 ± 124.1 $\times 10^9$/L; $F = 0.08$, $p = 0.920$), nor did splenic size ($F = 0.57$, $p = 0.566$) or bone marrow blasts ($F = 0.27$, $p = 0.764$). Smokers and non-smokers likewise showed comparable TLC (179.4 ± 124.5 vs 189.3 ± 117.5 $\times 10^9$/L; $t = -0.37$, $p = 0.711$), splenic size (23.0 ± 2.4 vs 22.3 ± 3.5 cm; $t = 1.19$, $p = 0.240$), bone marrow blasts (4.34 ± 2.30 vs 4.01 ± 2.28%; $t = 0.67$, $p = 0.507$), and peripheral blood blasts (2.41 ± 2.04 vs 3.00 ± 2.42%; $t = -1.26$, $p = 0.213$). These null findings suggest that, in this sample, hematologic tumor burden at presentation was determined predominantly by disease biology rather than by the exposure variables under study. Detailed comparisons are presented in Table 2.

Table 2. Association of Predictors with Disease Burden Markers

Predictor / Group	TLC, $\times 10^9$/L (Mean±SD)	Spleen size, cm (Mean±SD)	BM blasts, % (Mean±SD)	Test statistic	p-value
Occupation: High	181.6 ± 111.8	22.3 ± 3.1	4.15 ± 2.20	$F = 0.08$	0.920
Occupation: Moderate	178.4 ± 110.9	21.6 ± 4.4	3.65 ± 2.02	(df = 2,107)	
Occupation: Low	190.1 ± 124.1	22.7 ± 3.1	4.15 ± 2.36		
Smoker	179.4 ± 124.5	23.0 ± 2.4	4.34 ± 2.30	t = -0.37 / 1.19 / 0.67	0.711 / 0.240 / 0.507
Non-smoker	189.3 ± 117.5	22.3 ± 3.5	4.01 ± 2.28	(TLC / Spleen / BM blasts)	

Note. F = one-way ANOVA statistic (occupational exposure, df = 2,107); t = independent-samples t-test statistic (smoker vs non-smoker).

3.3 Predictors and Cardiac Outcomes

Overall, cardiac dysfunction, as defined by the composite study outcome, was present in 82 patients (74.5%). The mean EF was 63.1 ± 4.5%, and only one patient (0.9%) met the reduced-EF criterion (EF <50% or >10% reduction from baseline). Diastolic dysfunction (grade 1–2) was the most common abnormality, occurring in 51 patients (46.4%), followed by significant valvular regurgitation in 27 patients (24.5%) and pulmonary hypertension in 10 patients (9.1%). On bivariate analysis, the

prevalence of cardiac dysfunction differed significantly across occupational exposure categories (high: 84.6%, moderate: 46.2%, low: 76.1%; $\chi^2 = 7.00$, df = 2, P = 0.030), but not according to smoking status (smokers: 75.9% vs. non-smokers: 74.1%; $\chi^2 = 0.04$, P = 0.850), geographic distribution (semi-urban/rural: 76.8% vs. urban: 72.2%; $\chi^2 = 0.11$, P = 0.741), familial cancer history (positive: 83.3% vs. negative: 72.1%; $\chi^2 = 0.73$, P = 0.394), or sex (female: 73.1% vs. male: 75.9%; $\chi^2 = 0.01$, P = 0.908). Patients with cardiac dysfunction were significantly older than those without cardiac dysfunction (52.8 ± 14.0 vs. 29.8 ± 8.2 years; t = 10.50, P < 0.001), suggesting that age may be an important confounder of the observed association between occupational exposure and cardiac dysfunction. Full stratified results are presented in Table 3 and Figure 1, which illustrates the prevalence of cardiac dysfunction according to occupational exposure level and smoking status.

Table 3. Cardiac Outcomes Stratified by Exposure and Epidemiologic Predictors

Predictor	Cardiac dysfunction, n (%)	Test statistic	p-value
Occupational exposure		$\chi^2 = 7.00$, df = 2	0.030*
High	22/26 (84.6%)		
Moderate	6/13 (46.2%)		
Low	54/71 (76.1%)		
Smoking status		$\chi^2 = 0.04$, df = 1	0.850
Smoker	22/29 (75.9%)		
Non-smoker	60/81 (74.1%)		
Geography		$\chi^2 = 0.11$, df = 1	0.741
Urban	39/54 (72.2%)		
Semi-urban/Rural	43/56 (76.8%)		
Familial cancer history		$\chi^2 = 0.73$, df = 1	0.394
Positive	20/24 (83.3%)		
Negative	62/86 (72.1%)		
Sex		$\chi^2 = 0.01$, df = 1	0.908
Male	44/58 (75.9%)		
Female	38/52 (73.1%)		
Age (t-test, dysfunction vs none)	52.8±14.0 vs 29.8±8.2 y	t = 10.50	<0.001*

*Note. χ^2 = Pearson chi-square statistic; t = independent-samples t-test statistic (age). *p < 0.05.*

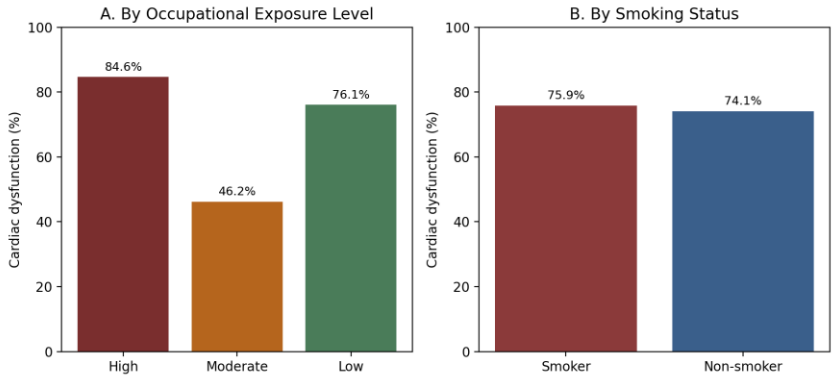

Figure 1. Prevalence of cardiac dysfunction by (A) occupational exposure level and (B) smoking status.

3.4 Correlation Analysis

Splenic size correlated positively with TLC (Spearman r = 0.24, p = 0.012), consistent with greater tumor mass accompanying higher leukocyte burden. Age correlated negatively with EF% (Pearson r = -0.37, p <0.001), as did bone marrow blast percentage (Spearman r = -0.27, p = 0.004). Splenic size showed a weaker inverse trend with EF% that did not reach significance (Spearman r = -0.18, p = 0.062), while TLC (r = -0.06, p = 0.522) and current-smoking status (r = -0.12, p = 0.229) were not significantly correlated with EF%. These relationships are illustrated in Figure 2, panel A (splenic size vs TLC) and panel B (age vs EF%).

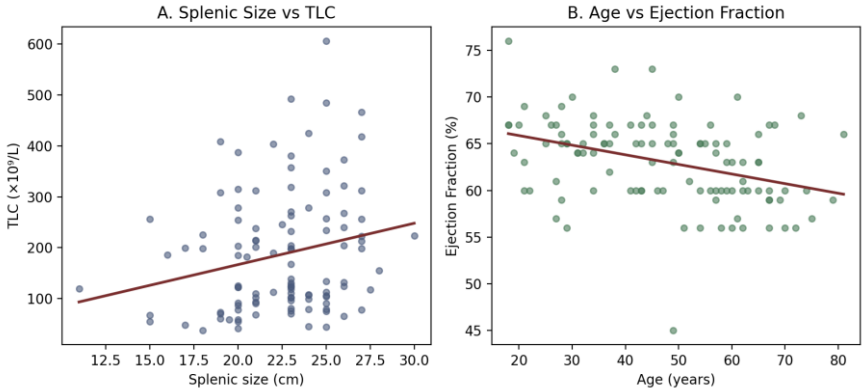

Figure 2. (A) Correlation between splenic size and total leukocyte count (TLC). (B) Correlation between age and ejection fraction (EF%). Lines represent linear trend.

3.5 Multivariable Regression Models

On multivariable logistic regression for cardiac dysfunction (adjusted for smoking, occupational exposure, geography, family history, sex, and age), age was the only independent predictor (OR = 1.19, 95% CI: 1.11-1.27, p <0.001), indicating an approximately 19% increase in the odds of cardiac dysfunction per additional year of age. High occupational exposure showed a non-significant trend toward increased risk relative to the low-exposure reference group (OR = 4.39, 95% CI: 0.56-34.61, p = 0.160), while current/ex-smoking (OR = 0.30, 95% CI: 0.05-1.88, p = 0.197), moderate exposure (OR = 0.34, p = 0.259), urban residence (OR = 1.26, p = 0.738), positive family history (OR = 3.23, p = 0.178), and male sex (OR = 3.96, p = 0.138) were not independently associated (model pseudo-R^2 = 0.52; likelihood-ratio p <0.001). On linear regression for EF%, age was again the only independent predictor (β = -0.093, 95% CI: -0.145 to -0.042, p = 0.001); smoking (β = -1.80, p = 0.103), bone marrow blasts (β = -0.29, p = 0.115), and splenic size (β = -0.19, p = 0.136) showed consistent negative but non-significant trends, while TLC and occupational category were not associated with EF% (model R^2 = 0.234, adjusted R^2 = 0.182, F = 4.46, p <0.001). Full regression output, including all covariate estimates and 95% CIs, is presented in Table 4.

Table 4. Multivariable Regression Analysis of Factors Associated With Cardiac Dysfunction and Ejection Fraction

Predictor	OR	95% CI	p	β (EF%)	95% CI	p
Age (per year)	1.19	1.11–1.27	<0.001*	-0.093	-0.145 to -0.042	0.001*
Current/ex-smoking	0.30	0.05–1.88	0.197	-1.80	-3.97 to 0.37	0.103
High occupational exposure†	4.39	0.56–34.61	0.160	-0.27	-2.68 to 2.14	0.822
Moderate occupational exposure†	0.34	0.05–2.23	0.259	1.57	-1.09 to 4.22	0.241
Urban residence	1.26	0.33–4.88	0.738	—	—	—
Positive family history	3.23	0.59–17.74	0.178	—	—	—
Male sex	3.96	0.64–24.44	0.138	—	—	—
Bone marrow blasts, %	—	—	—	-0.286	-0.642 to 0.071	0.115
Splenic size, cm	—	—	—	-0.191	-0.444 to 0.061	0.136
TLC, $\times 10^9$/L	—	—	—	0.001	-0.006 to 0.008	0.759

*Note. Left columns: logistic regression, outcome = cardiac dysfunction (yes/no), OR = odds ratio; reference categories = non-smoker, low occupational exposure. Right columns: linear regression, outcome = EF% (continuous), β = unstandardized coefficient. †Reference category = Low occupational exposure. *p < 0.05.*

4. DISCUSSION

The present cross-sectional study evaluated the relationships of smoking, occupation-based exposure, geographic residence, and familial cancer history with hematologic disease burden and echocardiographic cardiac abnormalities in 110 Egyptian patients with chronic myeloid leukemia (CML). The principal finding was the high prevalence of the prespecified composite cardiac outcome, which was identified in 74.5% of participants. Importantly, this composite outcome was predominantly driven by diastolic and other echocardiographic abnormalities rather than reduced systolic function: mean EF was 63.1 ± 4.5%, and only one patient (0.9%) met the reduced-EF criterion. Grade 1–2 diastolic dysfunction was the most frequent abnormality (46.4%), followed by valvular regurgitation (24.5%) and pulmonary hypertension (9.1%). After multivariable adjustment, age was the only factor independently associated with the composite cardiac outcome and with EF%, whereas occupational exposure showed a significant association on bivariate analysis that was attenuated after adjustment.

Cardiac abnormalities and the predominance of diastolic dysfunction

The high prevalence of the composite cardiac outcome should be interpreted in the context of its broad prespecified definition. The present study did not demonstrate a high prevalence of overt systolic dysfunction; rather, most abnormalities were related to diastolic function or other echocardiographic findings. This distinction is clinically important because a composite outcome encompassing several echocardiographic abnormalities should not be interpreted as equivalent to symptomatic heart failure or reduced left ventricular systolic function. Cardiovascular abnormalities have been increasingly recognized among patients with CML, reflecting potentially overlapping contributions from the underlying hematologic disease, conventional cardiovascular risk factors, age, and treatment exposure. Previous literature has described cardiovascular and vascular complications in patients receiving TKIs, including arterial events and other cardiovascular toxicities, with risk varying among individual agents [3,5,11-15]. However, the present study did not collect information regarding TKI type, treatment duration, dose, or cumulative exposure. Consequently, the observed echocardiographic abnormalities cannot be attributed specifically to TKI therapy, and the current findings should be interpreted as associations with cardiac abnormalities rather than evidence of treatment-related cardiotoxicity.

The predominance of diastolic abnormalities also warrants consideration of the strong influence of age. Age was substantially higher among participants with cardiac dysfunction than among those without dysfunction, and age remained independently associated with both the composite cardiac outcome and EF% in the multivariable analyses. Age-related changes in ventricular relaxation and myocardial compliance are well established in the general population [16,17]. Therefore, some of the echocardiographic abnormalities observed in this cohort may reflect age-related cardiovascular remodeling occurring in parallel with CML rather than a disease-specific cardiac effect. This finding emphasizes the importance of age as a major confounder when evaluating cardiovascular abnormalities in patients with hematologic malignancies.

Age as the principal independent factor

Age was the strongest and most consistent independent factor associated with the cardiac outcomes examined in this study. In the logistic regression model, each additional year of age was associated with higher odds of meeting the composite cardiac dysfunction definition (OR 1.19, 95% CI 1.11–1.27; P < 0.001). Similarly, age was independently associated with lower EF% in the linear regression model (β = −0.093, 95% CI −0.145 to −0.042; P = 0.001). These findings are biologically plausible and consistent with established age-related changes in cardiac structure and function [16,17]. Older patients may also have accumulated cardiovascular risk factors or longer exposure to disease- and treatment-related factors. In CML populations, cardiovascular risk assessment is particularly relevant because treatment-related vascular toxicity and pre-existing cardiovascular disease may coexist [3,5,18,25]. Nevertheless, because this study lacked longitudinal cardiovascular measurements and detailed treatment histories, the observed age association should not be interpreted as evidence that age itself causes cardiac dysfunction in CML. The strength and consistency of the age association also provide an important interpretation of the other findings. Several exposure variables showed directionally unfavorable estimates but did not remain statistically significant after adjustment. This pattern suggests that part of their apparent crude association may reflect differences in age or other correlated characteristics between exposure groups. The results therefore reinforce the importance of controlling for age when examining environmental and lifestyle factors in CML populations.

Smoking and cardiac outcomes

Smoking was not significantly associated with the composite cardiac outcome in either the bivariate analysis or the multivariable logistic regression. Similarly, the negative direction of the association between smoking and EF% did not reach statistical significance in the linear regression model. These findings should not be interpreted as evidence that smoking has no cardiovascular effect. Cigarette smoking is a well-established contributor to endothelial dysfunction, oxidative stress, vascular injury, and atherothrombotic disease [19,20]. The absence of statistical significance in the present study may reflect the relatively small number of smokers and the limited statistical power available for detecting modest independent effects after adjustment. In addition, current and former smokers were combined because of the small number of former smokers, which prevented assessment of dose, duration, pack-years, or the potential effects of smoking cessation. Therefore, the present analysis is best interpreted as showing no statistically demonstrable independent association within this cohort rather than evidence against the established cardiovascular effects of tobacco exposure.

Occupational exposure

Occupational exposure was significantly associated with the composite cardiac outcome on bivariate analysis. Cardiac dysfunction was present in 84.6% of participants classified as having high occupational exposure compared with 76.1% in the low-exposure group, although the moderate-exposure group had a lower prevalence (46.2%). After multivariable adjustment, the high-exposure category retained a directionally elevated odds ratio relative to the low-exposure reference group, but the association was no longer statistically significant (OR 4.39, 95% CI 0.56–34.61; P = 0.160). This attenuation after adjustment, together with the relatively wide confidence interval, indicates substantial uncertainty around the independent contribution of occupational exposure. The findings therefore do not establish that occupational exposure causes cardiac dysfunction. The occupation categories were predefined as proxies for presumed exposure rather than based on direct measurement of specific chemicals, pesticides, solvents, particulates, or other agents. Consequently, exposure misclassification is possible. Nevertheless, the direction of the association provides a potentially relevant hypothesis for future research. Occupational exposures such as pesticides, solvents, and other environmental agents have previously been investigated in relation to hematologic malignancies and cardiovascular or vascular effects [7,21,22]. The present study cannot identify which specific occupational agents, if any, contributed to the observed cardiac findings. Prospective studies incorporating quantitative exposure assessment, occupational histories, duration of exposure, and biomonitoring would be required to address this question more directly.

Disease burden and exposure variables

Neither smoking nor occupational exposure was significantly associated with the major hematologic or tumor-burden measures examined in this cohort. TLC, splenic size, bone marrow blast percentage, and peripheral blood blast percentage did not differ significantly according to smoking status, and the occupational exposure categories were similarly not associated with the evaluated disease-burden measures. These findings suggest that, within this sample, the observed variation in hematologic disease burden was not clearly explained by the exposure variables examined. However, the cross-sectional design and limited sample size prevent conclusions regarding whether these factors influence disease development, progression, treatment response, or long-term disease control. Hematologic indices represent a snapshot of disease status and may be influenced by disease phase, treatment, timing of assessment, and other clinical variables. The positive correlation between splenic size and TLC is biologically coherent because both may reflect hematologic disease burden. Conversely, the negative correlation between age and EF% and the weaker inverse association between bone marrow blasts and EF% should be interpreted cautiously, particularly because correlation does not establish temporal or causal relationships.

Geographic distribution and familial cancer history

No significant associations were identified between geographic residence and either disease-burden measures or cardiac outcomes. The geographic variable was defined according to the prespecified study protocol as urban versus semi-urban/rural residence and should therefore be regarded as a broad geographic proxy rather than a direct measurement of environmental exposure, socioeconomic status, healthcare access, or population-level environmental risk. Similarly, familial cancer history was not significantly associated with the cardiac outcome. The absence of an association with familial cancer history is not unexpected in the context of CML, which is generally driven by acquired BCR-ABL1-related molecular abnormalities rather than a common inherited familial cancer predisposition [1,8,24]. However, the familial-history variable in this study was designed to capture a broad history of hematologic or solid malignancy among first- or second-degree relatives. It was not

intended to establish a hereditary CML syndrome or a specific genetic predisposition. Therefore, these findings should not be interpreted as demonstrating that family history is clinically irrelevant to cancer counseling.

Clinical implications

The findings have potential implications for cardiovascular assessment in patients with CML. Current cardio-oncology guidance emphasizes baseline cardiovascular risk assessment and appropriate monitoring during cancer therapy, particularly when therapies with recognized cardiovascular toxicity are used [25]. The strong association between age and the composite cardiac outcome in this cohort supports careful consideration of age and cardiovascular risk when evaluating patients with CML. However, the present study does not provide sufficient evidence to recommend universal periodic echocardiographic screening for every patient with CML. The high prevalence of the composite outcome was largely driven by mild-to-moderate diastolic and other echocardiographic abnormalities, while reduced EF was uncommon. Furthermore, the clinical significance of all components of the composite outcome and their impact on subsequent cardiovascular events were not assessed longitudinally. A more appropriate implication is that cardiovascular assessment should be individualized according to age, baseline cardiovascular risk, clinical symptoms, and treatment-related risk, consistent with established cardio-oncology principles [25]. Smoking cessation should continue to be encouraged based on its established cardiovascular benefits, although the present study does not establish an independent association between smoking and the cardiac outcomes examined.

Strengths

This study has several strengths. First, it integrated hematologic disease-burden measures with multidimensional echocardiographic assessment rather than relying solely on EF. Second, the exposure variables were defined according to a prespecified classification scheme, allowing systematic comparison across occupational and geographic categories. Third, both bivariate and multivariable analyses were performed, allowing the strong influence of age to be distinguished from crude associations involving occupational exposure and other factors. Fourth, the inclusion of participants from different Egyptian governorates provided geographic diversity within the study population. Finally, the study followed the general principles of the STROBE framework for reporting observational research [10].

Limitations

Some limitations should be considered. detailed TKI treatment information, including the specific agent, treatment duration, dose regimen, and cumulative exposure, was unavailable. This limitation is particularly important because several TKIs have recognized cardiovascular and vascular toxicity profiles [3,5,11-15]. Consequently, the present study cannot separate potential disease-related cardiac abnormalities from treatment-related effects. the sample size of 110 patients and the relatively small moderate-exposure subgroup (n = 13) limited statistical power for detecting modest independent associations and resulted in wide confidence intervals for some regression estimates. Finally, this was a one-country cohort recruited from secondary and tertiary healthcare settings, which may limit generalizability to other populations and healthcare systems.

Overall interpretation

Taken together, the findings indicate that echocardiographic cardiac abnormalities were common in this cohort of Egyptian patients with CML, but overt systolic dysfunction was uncommon. Age was the most consistent independent factor associated with the cardiac outcomes examined. Occupational exposure showed a significant crude association with the composite cardiac outcome but did not retain statistical significance after multivariable adjustment, while smoking demonstrated no statistically significant independent association despite directionally unfavorable estimates for EF%. These findings support further investigation of cardiovascular health in CML, particularly in older patients and in populations with substantial occupational or environmental exposures. However, the present study should be considered hypothesis-generating with respect to occupational and smoking-related cardiac effects. Larger prospective multicenter studies incorporating detailed cardiovascular risk profiles, quantitative occupational exposure assessment, specific TKI type and duration, and serial echocardiographic evaluation are needed to determine the temporal and independent contributions of these factors to cardiovascular outcomes in CML.

5. CONCLUSION

In this cohort of patients with chronic myeloid leukemia, age was the strongest independent factor associated with the prespecified composite cardiac outcome, while occupational exposure showed an association on bivariate analysis that was attenuated after multivariable adjustment. The high prevalence of the composite cardiac outcome was predominantly

attributable to diastolic and other echocardiographic abnormalities rather than reduced EF. These findings support increased attention to cardiovascular assessment in patients with CML, particularly among older patients and those with relevant exposure histories. Prospective studies with detailed TKI exposure data, cardiovascular risk-factor assessment, and longitudinal echocardiographic follow-up are needed to determine the clinical significance of these abnormalities and to establish appropriate cardiac surveillance strategies.

DECLARATIONS

Ethics Approval and Consent to Participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Institutional Review Board approval was obtained from the Faculty of Medicine, Al-Azhar University, Egypt. Written informed consent was obtained from all participants before inclusion in the study. Patient confidentiality was maintained through anonymization of the analyzed clinical data.

Data Availability Statement

The anonymized datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare that they have no conflicts of interest related to this study.

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Declaration of Use of Artificial Intelligence

During the preparation of this manuscript, the authors used artificial intelligence (AI)-based tools solely for language editing, grammar and style improvement, organization of the manuscript, and assistance with the clarity of presentation. AI tools were not used to generate, analyze, or interpret the study data, perform statistical analyses, or determine the scientific conclusions. All scientific content, data interpretation, references, and final decisions regarding the manuscript were reviewed and verified by the authors. The authors take full responsibility for the accuracy, integrity, and originality of the submitted work.

Author Contributions:

All authors contributed to study conception and design, data acquisition, statistical analysis, manuscript drafting, and critical revision. All authors have approved the final version for submission

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