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# Modeling Competing Risks in Leukemia Patients: A Survival using the Cause-Specific Hazard Approach

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**ABSTRACT**

Leukemia is a hematological malignancy with high mortality, where deaths may arise from leukemia or other causes, leading to competing risks. This study aims to model event-specific mortality by integrating the Extended Cox model with time-dependent covariates into the Cause-Specific Hazard (CSH) framework. Secondary data from 130 leukemia patients at RSUD dr. H. Koesnadi Bondowoso (2022–2024) were analyzed, with survival time as the response and two competing events. Parameter estimation was conducted using maximum partial likelihood within a competing risks structure, optimized via Newton–Raphson iteration. The results show that chronic disease significantly increases the hazard of leukemia-related death (HR = 4.60; 95% CI: 1,46-14,44), while sex (HR = 0.30; 95% CI: 0,12-0,73) and body mass index (HR = 0.82; 95% CI: 0,73-0,91) significantly influence mortality due to other causes. These findings demonstrate that the CSH framework provides more accurate and clinically interpretable estimates by distinguishing event-specific risks. This approach supports improved risk stratification and evidence-based clinical decision-making in leukemia management.



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## 1. INTRODUCTION

Leukemia is a type of blood cancer characterized by the abnormal proliferation of white blood cells and remains a significant cause of mortality worldwide [1]. It is one of the leading causes of cancer-related death, especially in children and people of productive age [2]. The Global Burden of Disease study records hundreds of thousands of new leukemia cases annually with significant mortality rates, particularly in developing countries [3]. In Indonesia, leukemia ranks among the top ten cancers with the highest prevalence and is the most common childhood cancer [4]. The high mortality rate in leukemia patients is influenced by various factors, including delayed diagnosis, limited access to healthcare services, and comorbidities such as infections and chronic diseases [2].

In biostatistics, survival analysis is commonly used to examine time-to-event data, with the Cox Proportional Hazards (Cox PH) model being widely applied due to its semi-parametric nature and minimal distributional assumptions [5]. However, in leukemia cases, patient outcomes may involve more than one type of event, such as death due to leukemia progression or death due to other causes, including infections or treatment-related complications. This condition is referred to as competing risk, where the occurrence of one type of event prevents the occurrence of another [6]. Ignoring competing risks can lead to biased estimation and incorrect clinical interpretation, particularly in medical studies involving multiple causes of failure [7]. Therefore, more appropriate analytical approaches are required to obtain accurate and clinically relevant results [8].

To address this limitation, competing risk approaches such as the Fine–Gray model and the Cause-Specific Hazard (CSH) model have been developed [9]. The CSH model allows the estimation of hazard functions for each event type separately by treating competing events as censored observations, thereby providing more specific information on the effects of covariates for each type of event [10]. In addition to the Cause-Specific Hazard model, the Fine Gray model is also widely used to directly model the cumulative incidence function in the presence of competing risks [11]. Previous studies have demonstrated that competing risk models provide more reliable and interpretable risk estimates compared to the conventional Cox model in leukemia cases [12]. In addition, recent developments in survival analysis have emphasized the importance of competing risk approaches in improving prediction accuracy and clinical interpretation in oncology research [13]. Other things include highlighted the robustness of competing risk survival models in clinical datasets [14]. Furthermore, competing risk frameworks have been widely applied across various cancer types, reinforcing their importance in modern survival analysis [15].

Despite these advancements, the application of competing risk models-particularly the Cause-Specific Hazard model with time-dependent covariates-remains limited in leukemia studies in Indonesia. Most existing studies still rely on conventional survival analysis without explicitly accounting for competing events, potentially resulting in biased estimations. Furthermore, the use of regional hospital data is still limited, even though such data are important for capturing local patient characteristics and healthcare constraints. From a methodological perspective, this study proposes the integration of time-dependent covariates into the Cause-Specific Hazard framework using an Extended Cox model, allowing the effects of predictors to vary over time while maintaining cause-specific interpretation. Therefore, the research question is: how do clinical and demographic factors influence event-specific mortality risks in leukemia patients under a competing risks framework with time-dependent effects? This study aims to identify significant predictors of cause-specific mortality and provide more accurate and clinically relevant risk estimation to support clinical decision-making and healthcare resource allocation.

## 2. RESEARCH METHOD

The research uses secondary data from medical records of 130 leukemia patients treated at RSUD dr. H. Koesnadi Bondowoso from January 2022 to December 2024. The response variable was patient survival time measured in months, defined as the interval from the patient's first leukemia diagnosis to the occurrence of an event or the end of the observation period. Event status was classified into three categories: censored data (if the patient was still alive at the end of the observation period or lost to follow-up), event type 1 (death due to leukemia), and event type 2 (death due to other causes), with the latter serving as competing events. Predictor variables included age, sex, platelet count, hemoglobin level, bone marrow blast count, genetic mutation status, infection history, body mass index (BMI), and chronic disease. Patients were followed from diagnosis until event occurrence or the end of the study, with censoring defined as alive at the end of follow-up, lost to follow-up, or competing events. Given the relatively small sample size (n = 130) compared to the number of predictors, model complexity was carefully controlled by restricting the final multivariable model to clinically relevant variables and interpreting exploratory interaction analyses cautiously. The interaction models were intended to identify potential pairwise patterns rather than to construct a definitive predictive model. Therefore, the reported interaction results should be interpreted as exploratory findings requiring further validation in larger multicenter datasets

Data analysis was performed using a survival analysis approach, a statistical method used to model the time until an event occurs, with the main characteristic being the presence of censored data. The initial analysis stage involved fitting a Cox Proportional Hazard (Cox PH) model, a semi-parametric model where an individual's hazard function is the product of the baseline hazard and an exponential function of covariates [16]. The mathematical formulation of the Cox Proportional Hazards model adopted in this study follows the formulation presented by Collett [16]:

$$h(t|X) = h_0(t)e(\beta^T X) \tag{1}$$

where $h(t|X)$ is the hazard function at time t, $h_0(t)$is the baseline hazard, and β is the vactor of regression coefficients. This model was chosen because it does not require a specific distributional assumption for survival

time and is widely used in epidemiological and clinical research. The main assumption of the Cox PH model is proportional hazards, meaning the hazard ratio between individuals is constant over time [17]. This assumption was tested using Schoenfeld residuals [18]. When the proportional hazards assumption is not satisfied, the Extended Cox model is applied by incorporating time-dependent covariates, allowing the effects of predictors to vary over time. The Extended Cox model formulation with time-dependent covariates also follows the approach described by Collett [16]:

$$h(t|X(t)) = h_0(t)e(\beta X + \gamma X(t)) \quad (2)$$

where $X(t)$ represents time-dependent covariates and $\gamma$ denotes the corresponding coefficients capturing time-varying effects. In this study, time-dependency was modeled using interaction terms between covariates and time, particularly for variables that violated the proportional hazard assumption. With in the competing risks framework, these time-dependent covariates are included in each cause-specific hazard function to capture their dynamic influence on different types of events [16].

In leukemia data, patient death can occur due to leukemia itself or other causes such as severe infection or organ complications, meaning there is more than one type of competing event. This condition is known as competing risk, where the occurrence of one event prevents the occurrence of another [10]. To accommodate this condition, the research used the Cause-Specific Hazard (CSH) model, an extension of Cox regression that models the hazard separately for each event type by treating other events as censored [5]. Recent methodological developments have further improved the application of competing risk models in biomedical studies, particularly in oncology datasets where multiple failure types frequently occur [19]. The Cause-Specific Hazard (CSH) model used in this study was formulated based on the competing risks framework described by Collett [16]:

$$h_k(t|X) = h_{0k}(t)\, e(\beta_k^T X) \quad (3)$$

Where $h_{k0}(t)$ denotes the baseline hazard for the k-th event, $\beta_k$ is the regression parameter vector, and X represents covariates. The concordance index (C-index) was used to evaluate the predictive performance of the Cause-Specific Hazard model, calculated based on the apparent fitted model without additional external or bootstrap validation [20]. The final model produced an apparent C-index of 0.721 for event type 2 and values ranging from 0.567 to 0.735 across the exploratory pairwise interaction models. Parameter estimation in the Cox and Cause-Specific Hazard models was performed using the Maximum Partial Likelihood method, which allows estimation without specifying the baseline hazard function. The optimization process was carried out using the Newton–Raphson iterative algorithm [16]. The significance of the parameters was tested using the Wald test at a 5% significance level [21]. Statistically significant parameters were interpreted using hazard ratio values to explain the magnitude of the covariate's influence on the risk of event occurrence [22]. The overall interpretation of competing risks was then performed for the leukemia patient data.

## 3. RESULT AND ANALYSIS

Descriptive analysis was conducted to describe the characteristics of leukemia patients based on the research variables. The observed characteristics included age, sex, platelet count, hemoglobin level, bone marrow blast count, genetic mutation status, infection history, body mass index (BMI), and the presence of chronic disease. The results showed that the majority of patients were under 40 years old and were predominantly male. Most patients had platelet and hemoglobin levels in the normal range, but the proportion of patients with a high bone marrow blast count was substantial, indicating active disease. Clinically, the significant effect of chronic disease on mortality suggests the need for closer monitoring and integrated management of comorbidities in leukemia patients. These findings highlight the importance of early risk stratification to support more targeted treatment decisions and improve patient outcomes.

### 3.1 Data Exploration

The Cox Proportional Hazard Regression model was formed as an initial analysis to identify factors influencing leukemia patient survival time without distinguishing event types. The Cox regression model is as follows:

$$\begin{aligned} h(t,X) = h_0(t)\exp(&-0{,}520\ Age - 0{,}554\ \text{Sex} + 0{,}067\ \text{Platelet} - 0{,}594\ \text{Hemoglobin} \\ &+ 0{,}339\ \text{BMB} + 0{,}229\ \text{Genetic Mutation} + 0{,}720\ \text{Infection History} \\ &- 1{,}066\ \text{BMI} + 0{,}321\ \text{Chronic}) \end{aligned}$$

### 3.2 Proportional Hazard Assumption Test

**Table 1.** Proportional Hazard Assumption

| Variable | *p-value* | PH Assumption |
|---|---|---|
| Age | 0,260 | Satisfied |
| Sex | 0,438 | Satisfied |
| Platelet | 0,947 | Satisfied |
| Hemoglobin | 0,814 | Satisfied |
| **BMB** | **0,017** | **Not Satisfied** |
| Gen Mutation | 0,577 | Satisfied |
| Infection His | 0,139 | Satisfied |
| BMI | 0,389 | Satisfied |
| Chronic | 0,625 | Satisfied |

Table 1 shows that all predictor variables satisfied the proportional hazard assumption (p-value > 0.05), except for the Bone Marrow Blast (BMB) variable (p-value = 0.017). This result indicates that the effect of BMB on the hazard is not constant over time, thereby violating the proportional hazard assumption. To address this issue, an Extended Cox model was implemented by introducing a time-dependent component through an interaction between BMB and follow-up time ($BMB \times t$). The resulting model can be expressed as

$$h(t|x) = h_0(t)\exp\big(\beta_1 Age + \beta_2 Sex + \beta_3 Platelet + \beta_4 Hemoglobin + \beta_5 BMB + \beta_6 Gen\ Mutation + \beta_7 Infection\ History + \beta_8 BMI + \beta_9 Chronic + \gamma(BMB \times t)\big),$$

where $\gamma$ represents the coefficient associated with the time-varying effect of BMB. The estimated coefficient of the time-dependent component was 0.0139 with a p-value of 0.027, indicating a statistically significant time-varying effect. This finding confirms that the influence of Bone Marrow Blast on the hazard changes throughout the follow-up period rather than remaining constant. Therefore, the Extended Cox specification was retained in the subsequent Cause-Specific Hazard analysis to appropriately accommodate the observed non-proportional hazard effect and improve the validity and reproducibility of the competing risks model.

### 3.3 Cause-Specific Hazard

Cause-Specific Hazard Model for Event type 1 (due to leukemia)

**Table 2.** Cause-Specific Hazard Model for Event Type 1

| Variable | Coefficient | HR | SE | 95% CI Lower | 95% CI Upper | *p-value* |
|---|---|---|---|---|---|---|
| Age | 0,0112 | 1,0113 | 0,0098 | 0,9921 | 1,0318 | 0,250 |
| Sex | -0,2739 | 0,7603 | 0,6269 | 0,2226 | 2,5983 | 0,662 |
| Platelet | 0,000009 | 1,0000 | 0,000005 | 1,0000 | 1,0000 | 0,054 |
| Hemoglobin | 0,2129 | 1,2372 | 0,1579 | 0,9079 | 1,6861 | 0,178 |
| BMB | -0,0062 | 0,9938 | 0,0086 | 0,9772 | 1,0118 | 0,471 |
| Gen Mutation | 0,1523 | 1,1644 | 0,8199 | 0,2335 | 5,8080 | 0,853 |
| Infection His | 0,1155 | 1,1224 | 0,5981 | 0,3476 | 3,6256 | 0,847 |
| BMI | -0,0182 | 0,9819 | 0,0626 | 0,8685 | 1,1095 | 0,771 |
| Chronic | 1,5258 | 4,5988 | 0,5841 | 1,4637 | 14,4189 | 0,009 |

$$h_1(t,X) = h_1(t)\exp(0{,}0112\ \text{Age} - 0{,}2739\ \text{Sex} + 0{,}000009\ \text{Platelet} + 02129\ \text{Hemoglobin} - 0{,}0062\ \text{BMB} + 0{,}1523\ \text{Genetic Mutation} + 0{,}1155\ \text{Infection History} - 0{,}0182\ \text{BMI} + 1{,}5260\ \text{Chronic}$$

The simple Cause-Specific Hazard model for event type 1 is formed as,
$h_1(t,X) = h_1(t)\exp(1{,}5260\ \text{Chronic})$. The Cause-Specific Hazard model for event type 1 shows that only the Chronic Disease variable has a significant influence, with a hazard ratio of 4.5989. This indicates that patients with chronic disease have approximately 4.6 times higher risk of leukemia-related death compared to those without chronic disease. This result is statistically significant ($p < 0.05$), confirming the strong effect of comorbidity on event type 1.

### 3.4 Cause-Specific Hazard Model for Event type 2 (Competing risk)

**Table 3.**Cause-Specific Hazard Model for Event Type 2

| Variabel | Coefficient | HR | SE | 95% CI Lower | 95% CI Upper | *p-value* |
|---|---|---|---|---|---|---|
| Age | 0,0016 | 1,0016 | 0,0066 | 0,9888 | 1,0146 | 0,85 |
| Sex | -1,2130 | 0,2974 | 0,4575 | 0,1213 | 0,7291 | 0,008 |
| Platelet | 0,0000003 | 1,0000 | 0,000003 | 1,0000 | 1,0000 | 0,928 |
| Hemoglobin | 0,1322 | 1,1413 | 0,1122 | 0,9160 | 1,4220 | 0,239 |
| BMB | 0,0013 | 1,0013 | 0,0061 | 0,9894 | 1,0133 | 0,831 |
| Gen Mutation | -0,2570 | 0,7734 | 0,5182 | 0.2801 | 2,1354 | 0,620 |
| Infection His | 0,5813 | 1,7883 | 0,4390 | 0,7564 | 4,2277 | 0,185 |
| BMI | -0,2001 | 0,8187 | 0,0572 | 0,7398 | 0,9060 | 0,0001 |
| Chronic | -0,7000 | 0,4966 | 0,4693 | 0,1979 | 1,2460 | 0,136 |

The simple Cause-Specific Hazard model for event type 2 is formed as $h_2(t, X) = h_2(t)\exp(-1{,}2130\ \text{Age} - 0{,}2001\ \text{BMI})$. The Cause-Specific Hazard model for event type 2 shows that a hazard function is multiplicative to the baseline hazard $h_2(t)$.. The Sex and BMI variables have negative coefficients with hazard ratios < 1, indicating a decreased risk of event type 2, while Infection History shows a tendency for increased hazard although not statistically significant. The hazard ratio for sex (HR = 0.2974) indicates a substantially lower risk of event type 2 compared to the reference category, while BMI (HR = 0.8187) also shows a protective effect. Both variables are statistically significant ($p < 0.05$), indicating their important role in competing mortality.

The study involved nine predictor variables. To examine potential joint effects between predictors, pairwise interaction terms were explored within the Cause-Specific Hazard (CSH) framework, resulting in 36 possible two-way combinations. This exploratory step aimed to assess whether combinations of covariates jointly influence the risk of event occurrence for each event type. Due to the large number of combinations, the discussion in this subsection focuses on one representative pair, namely age and sex. For event type 1, the Cause-Specific Hazard model for the Age–Sex interaction is expressed as:

$$h_1(t|\text{Age}, \text{Sex}) = h_{01}(t)\exp(0{,}0042\ \text{Age} - 0{,}3516\ \text{Sex}).$$

For event type 2, the corresponding model is:

$$h_2(t|\text{Age}, \text{Sex}) = h_{02}(t)\exp(-0{,}0004\ \text{Age} - 0{,}3919\ \text{Sex})$$

The predictive performance of each model was assessed using the concordance index (C-index), where higher values indicate better discrimination ability. From the exploratory analysis of pairwise combinations, certain variable pairs such as Sex vs BMI, Platelet vs Chronic, and BMI vs Chronic showed relatively stronger associations with the hazard compared to other combinations. A total of 36 possible pairwise combinations were generated from the nine predictor variables included in the study. Tables 4–6 present only three representative combinations selected from the exploratory analysis because they demonstrated relatively stronger associations and higher concordance index values compared to other combinations. These tables are intended solely to illustrate representative interaction patterns within the exploratory Cause-Specific Hazard analysis and do not represent the complete set of evaluated combinations.

**Table 4.** Sex vs BMI

| Event | HR | p-value | C |
|---|---|---|---|
| 1 | 0,9584 | 0,439 | 0,567 |
| 2 | 0,8465 | 0,000106 | 0,721 |

Table 4 indicates that the Sex vs BMI variable pair shows a statistically significant association with the risk of event occurrence for event type 2, as evidenced by a p-value < α. In addition, the concordance value ≥ 0. suggests that this variable pair has acceptable predictive ability. Among the 36 evaluated pairwise combinations, the Sex vs BMI interaction was selected as a representative example because it demonstrated one of the strongest associations and the highest concordance value for event type 2.

**Table 5.** Platelet vs Chronic

| Event | HR | p-value | C |
|---|---|---|---|
| 1 | 5,269 | 0,0018 | 0,735 |
| 2 | 0,9698 | 0,940 | 0,589 |

Table 5 indicates that the Platelet vs Chronic Disease variable pair shows a statistically significant association with the risk of event occurrence for event type 1, as evidenced by a p-value < α. The hazard ratio > 1 suggests an increased risk associated with this variable pair, while the concordance value ≥ 0.65 indicates acceptable

predictive ability. Among the evaluated pairwise combinations, Platelet vs Chronic Disease was selected as a representative interaction because it showed a relatively strong association and acceptable predictive discrimination for event type 1.

**Table 6.** BMI vs Chronic

| Event | HR | p-value | C |
|---|---|---|---|
| 1 | 3,6098 | 0,0066 | 0,722 |
| 2 | 0,6419 | 0,2719 | 0,687 |

Table 6 indicates that the BMI vs Chronic Disease variable pair shows a statistically significant association with the risk of event occurrence for event type 1, as evidenced by a p-value $< \alpha$. The hazard ratio $> 1$ suggests an increased risk associated with this variable pair, while the concordance value $\geq 0.65$ indicates acceptable predictive ability. BMI vs Chronic Disease was included as another representative exploratory interaction because it demonstrated relatively higher hazard discrimination compared to several other evaluated combinations. Because the interaction analysis was exploratory and intended only to identify potential pairwise patterns among predictors, formal model selection criteria such as $\Delta$AIC and bootstrap optimism correction were not used as the basis for final model construction. Therefore, the interaction models should be interpreted cautiously and not as confirmatory predictive models.

### 3.5 Parameter Estimation β

**Table 7.** Parameter Estimation

| Variable | Parameter |
|---|---|
| Age | $5{,}69 \times 10^{-3}$ |
| Sex | $-8{,}67 \times 10^{-1}$ |
| Platelet | $3{,}37 \times 10^{-6}$ |
| Hemoglobin | $1{,}47 \times 10^{-1}$, |
| BMB | $-1{,}62 \times 10^{-3}$ |
| Gen Mutation | $-1{,}49 \times 10^{-1}$ |
| Infection His | $4{,}48 \times 10^{-1}$, |
| BMI | $-1{,}16 \times 10^{-1}$ |
| Chronic | $1{,}61 \times 10^{-1}$, |

In Table 7, parameter estimation of the Cause-Specific Hazard model for leukemia patient mortality risk for all researched predictor variables, namely age, sex, platelet count, hemoglobin, bone marrow blast count, genetic mutation, infection history, BMI, and chronic disease. The parameter estimation results describe the direction and magnitude of the influence of each variable on specific mortality hazard. The log partial likelihood value of $-170.34$ indicates the model's fit to the data and is used as a basis for model evaluation and comparison in the competing risk analysis of leukemia patient mortality. The predictive performance was assessed using the concordance index (C-index), reported as an apparent estimate without optimism correction, which may lead to overestimation of model performance. The apparent C-index values indicated acceptable discriminatory ability for several exploratory interaction models, particularly Platelet vs Chronic Disease (C = 0.735), BMI vs Chronic Disease (C = 0.722), and Sex vs BMI for event type 2 (C = 0.721). In addition to parameter estimation, diagnostic evaluation of the proportional hazard assumption was performed using Schoenfeld residuals. Figure 1 presents the Schoenfeld residual plots for the predictor variables included in the final Cause-Specific Hazard model. These diagnostic plots were used to assess whether the residual patterns exhibited systematic time-dependent trends that could indicate violations of the proportional hazard assumption.

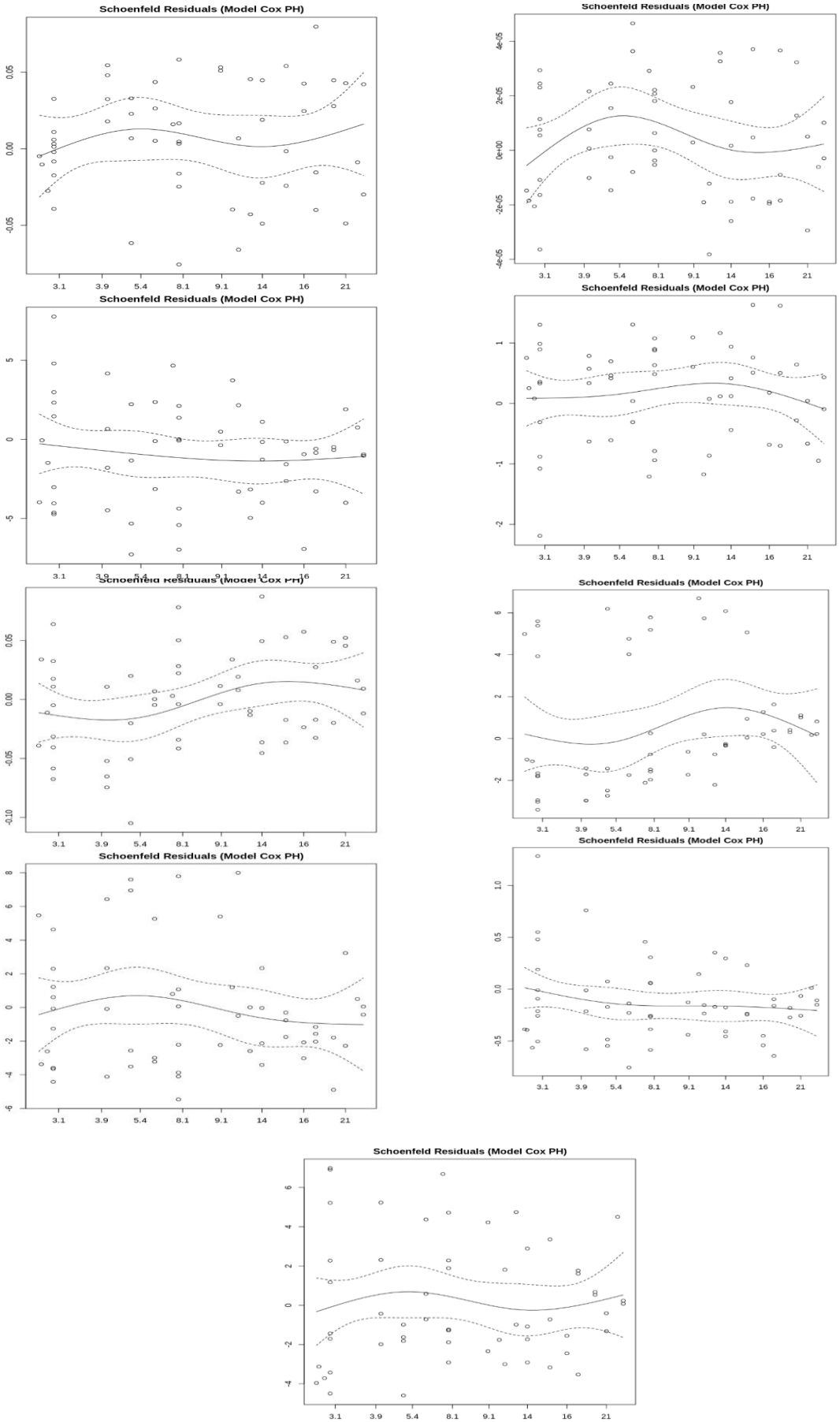


**Figure 1**. Schoenfeld Residual Plots for the Final Cause-Specific Hazard Model

Based on Figure 1, the Schoenfeld residual plots for all predictor variables show residual points that are randomly dispersed around the horizontal reference line with no strong monotonic or systematic time-dependent pattern. The fitted smoothing curves remain relatively stable over the follow-up period and generally stay within the corresponding confidence bands, indicating that the effects of the covariates do not substantially vary over time. Although minor local fluctuations are observed in several variables, these variations are not sufficiently pronounced to indicate serious departures from the proportional hazard assumption. Therefore, the Schoenfeld residual diagnostics suggest that the proportional hazard assumption is reasonably satisfied for the final Cause-Specific Hazard model, supporting the validity and adequacy of the estimated hazard ratios for interpreting event-specific mortality risk in leukemia patients under the competing risks framework. Consequently, the final model was considered statistically appropriate for subsequent parameter interpretation and competing risk analysis.

### 3.6 Parameter Testing

**Table 8.** Parameter Testing

| Variable | $W^2$ | p-value | Decision |
|---|---|---|---|
| Age | 1,08 | 0,281 | Accepted $H_0$ |
| Sex | **-2,39** | **0,017** | **Reject $H_0$** |
| Platelet | 1,24 | 1,217 | Accepted $H_0$ |
| Hemoglobin | 1,67 | 0,095 | Accepted $H_0$ |
| BMB | -0,33 | 0,739 | Accepted $H_0$ |
| Gen Mutation | -0,35 | 0,730 | Accepted $H_0$ |
| Infection His | 1,29 | 0,197 | Accepted $H_0$ |
| BMI | **-3,07** | **0,006** | **Reject $H_0$** |
| Chronic | 0,48 | 0,633 | Accepted $H_0$ |

Table 8 presents the results of the final multivariable Cause-Specific Hazard model, where all predictor variables are included simultaneously. This model differs from previous analyses, which were conducted separately for each event type. The joint estimation approach explains the differences in p-values observed across tables.

### 3.7 Hazard Ratio

Hazard ratio is a measure describing the magnitude of a predictor variable's influence on the risk of an event occurring at a specific time, assuming other covariates are constant. An HR value > 1 indicates an increased risk of the event, HR < 1 indicates a decreased risk, while HR = 1 indicates no influence. The dashed vertical line on the graph represents the HR = 1 value as the neutral threshold.

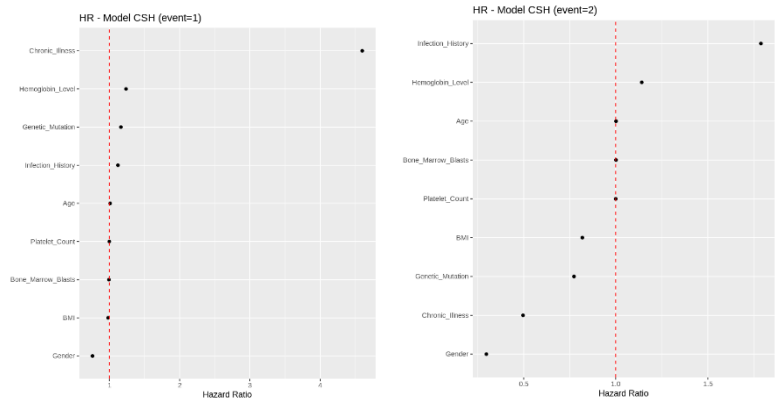


**Figure 2.** Hazard Ratio Type 1 and 2

Based on Figure 2. hazard ratio of the Cause-Specific Hazard model for event type 1 and type 2, chronic disease is the dominant risk factor for event type 1 with a hazard ratio value far above 1, indicating a significantly increased risk compared to patients without chronic disease. Hemoglobin, genetic mutation, and infection history variables have hazard ratios slightly above 1, indicating a tendency for increased risk, while age, platelet count, bone marrow blast count, and BMI have hazard ratios close to 1, showing no strong influence on event type 1, and sex is associated with a lower risk. For event type 2, infection history and hemoglobin show hazard ratios above 1, indicating an increased risk of event occurrence, while age, bone marrow blast count, and platelet count have hazard ratios close to 1, and BMI, genetic mutation, chronic disease, and sex are associated with a decreased risk compared to the reference category.

### 3.8 Discussion

This study shows that chronic disease is the primary determinant of leukemia-related mortality, as indicated by a substantially higher hazard ratio for event type 1. In contrast, sex and body mass index (BMI) are identified as significant factors influencing mortality due to competing causes. These findings highlight the importance of distinguishing between event types when analyzing survival data, as different predictors may influence different causes of death. These results are consistent with recent studies in oncology survival analysis, which emphasize the importance of competing risk approaches in identifying cause-specific determinants of mortality. Previous research has shown that comorbidities significantly increase the risk of disease-specific death, while demographic and physiological factors such as sex and BMI are more closely associated with non-disease-related mortality. Compared to conventional Cox models, the Cause-Specific Hazard approach provides more detailed insights into how different risk factors operate across competing events.

The effect of chronic disease on leukemia-related mortality may be explained by the reduced physiological resilience of patients with comorbid conditions, which can worsen disease progression and limit treatment effectiveness. Meanwhile, the influence of BMI and sex on mortality due to other causes may be associated with metabolic conditions, treatment-related toxicity, and hormonal differences that affect overall health status. These findings are clinically plausible and support the need for integrated patient management that considers both primary disease and comorbid conditions. This study has several limitations. First, the use of single-center data may limit the generalizability of the findings to broader populations. Second, the relatively small sample size compared to the number of predictors may increase the risk of overfitting, despite efforts to control model complexity. Third, potential unmeasured confounders, such as treatment variations and socioeconomic factors, were not included in the analysis. Additionally, the absence of external validation means that the predictive performance of the model may be optimistic. Additionally, if loss to follow-up was related to disease severity, informative censoring could introduce bias, which was not formally tested due to data constraints. Future research should involve multicenter datasets with larger sample sizes to improve generalizability and model robustness. The application of advanced statistical methods, such as penalized regression or machine learning approaches, is also recommended to enhance predictive accuracy. Furthermore, integrating competing risk models into clinical decision support systems may help improve risk stratification and optimize treatment planning for leukemia patients

## 4. CONCLUSION

The Cause-Specific Hazard framework provides more accurate and interpretable estimates of event-specific mortality compared to conventional Cox models in the presence of competing risks. Chronic disease is the dominant factor in leukemia-related death, while sex and BMI significantly influence mortality from other causes. These findings highlight the importance of incorporating competing risk analysis to avoid biased estimation. Practically, the results support improved comorbidity management, risk-based monitoring, and more effective clinical decision-making in regional healthcare settings.

## 5. REFERENCES


[1] D. G. Gilliland, C. T. Jordan, and C. A. Felix, 'The molecular basis of leukemia', *ASN Education*, vol. 1, no. 2, pp. 80–97, 2004, doi: 10.1182/asheducation-2004.1.80.

[2] M. H. Farrag, K. Ghazaly, R. Mohammed, B. Volland, H. Hero, and F. Berthold, 'Comparing presentations and outcomes of children with cancer: A study between a lower-middle-income country and a high-income country', *BMC Pediatr.*, vol. 23, no. 1, 2023, doi: 10.1186/s12887-023-03920-5.

[3] R. Sharma and C. Jani, 'Mapping incidence and mortality of leukemia and its subtypes in 21 world regions in last three decades and projections to 2030', *Ann. Hematol.*, vol. 101, no. 11, pp. 2449–2465, 2022, doi: 10.1007/s00277-022-04974-0.

[4] E. Cahyadi, M. C. S. Poespitangyas, D. K Arumsari, M. R. Larasati, and U. Andarsini, I. D. G Ugrasena, 'Region variation of hematological malignancies and solid tumors in children in East Java', *Asian Journal of Health Research*, vol. 2, no. 1, pp. 27–33, 2023.

[5] D. G. Kleinbaum and M. Klein, *Survival Analysis: A Self-Learning Text, 3rd ed.* New York: Springer, 2012. doi: 10.1007/978-1-4419-6646-9.

[6] B. N. Wiyoto and H. Sumarno, 'Competing risk analysis bagi pasien pneumonia di suatu rumah sakit', *MILANG Journal of Mathematics*, vol. 8, no. 2, pp. 99–114, 2022, doi: 10.29244/milang.18.2.99-114.

[7] M. Noordzij, 'When do we need competing risks methods for survival analysis in nephrology?', *Nephrology Dialysis Transplantation*, vol. 36, no. 6, pp. 961–965, 2021, doi: 10.1093/ndt/gfaa285.

[8] Z. Zhang, 'Survival analysis in the presence of competing risks', *Ann. Transl. Med.*, vol. 5, no. 3, 2017, doi: 10.21037/atm.2016.08.62.

[9] H. T. Kim, 'Competing risks data in clinical oncology', *Front. Oncol.*, vol. 14, no. 2, 2024, doi: 10.3389/fonc.

[10] T. A. Gooley, 'Estimation of failure probabilities in the presence of competing risks: New representations of old estimators', *Stat. Med.*, vol. 18, no. 6, pp. 695–706, 1999, doi: 10.1002/(sici)1097-0258(19990330)18:6<695::aid-sim60>3.0.co;2-o.

[11] T. A. Austin and P. C. Fine, 'Practical recommendations for reporting Fine-Gray model analyses for competing risk data', *Stat. Med.*, vol. 39, no. 27, pp. 4391–4400, 2020, doi: 10.1002/sim.8762.

[12] M. F. Majeed, 'Survival analysis for leukemia data using cox proportional hazard and competing risk models', *Journal of Applied Hematology*, vol. 15, no. 1, pp. 21–28, 2024, doi: 10.4103/joah.joah_45_23.

[13] Q. Zhang, 'Competing risk and random survival forest models for predicting survival in cancer patients', *Sci. Rep.*, vol. 15, no. 1, 2025, doi: 10.1038/s41598-025-05824-1.

[14] S. Liu, 'Application of competing risk survival models in clinical research', *Endocrine*, vol. 83, 2024, doi: 10.1007/s12020-023-03512-9.

[15] Y. Wang, 'Competing risk analysis in cancer prognosis: A multi-disease application', *Front. Oncol.*, vol. 13, 2023, doi: 10.3389/fonc.2023.996354.

[16] D. Collett, *Modelling Survival Data in Medical Research, 2nd ed.* USA: Chapman & Hall/CRC, 2003. doi: 10.1201/9781420035937.

[17] D. G. Kleinbaum and M. Klein, *Survival Analysis: A Self-Learning Text, 2nd ed.* New York: Springer, 2005. doi: 10.1007/978-1-4419-6646-9.

[18] P. M. Grambsch and T. M. Therneau, 'Proportional hazards tests and diagnostics based on weighted residuals', *Journal Biometrika*, vol. 81, no. 3, pp. 515–526, 1994, doi: 10.1093/biomet/81.3.515.

[19] S. Liu, 'Application of competing risk models in leukemia survival analysis', *BMC Med. Res. Methodol.*, vol. 22, 2022, doi: 10.1186/s12874-022-01585-5.

[20] F. E. Harrell, *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis, 2nd ed.* New Yor: Springer, 2015. doi: 10.1007/978-3-319-19425-7.

[21] D. W. Hosmer and S. Lemeshow, *Applied Survival Analysis: Regression Modeling of Time-to-Event Data.* New York: Wiley, 1999. doi: 10.1002/0471722146.

[22] Z. Zhang, 'Censoring issues in survival analysis', *J. Stat. Res.*, vol. 39, no. 1, pp. 1–16, 2005.