Pretreatment grade 4 thrombocytopenia is an independent prognostic factor in adult acute lymphoblastic leukemia: an extended analysis of a single-center retrospective study

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ABSTRACT

Objectives: Low pretreatment platelet count is negatively associated with overall survival (OS) of certain subtypes of acute lymphoblastic leukemia (ALL). However, the prognostic impact of the grade of thrombocytopenia on OS and disease-free survival (DFS) has never been explored.

Methods: We conducted an extended analysis of a retrospective study. Newly diagnosed adults with ALL was enrolled in this study. The grade of thrombocytopenia was evaluated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Prognostic impacts were assessed by the hazard ratios (HRs) and 95% confidence intervals (CIs) obtained from univariate and multivariate Cox proportional hazards regression analyses.

Results: A total of 90 participants were included in this study. There were 18 cases with grade 4 thrombocytopenia among the 71 participants presented with thrombocytopenia of any grade. Both univariate and multivariate Cox regression analyses suggested the independent negative prognostic impact of grade 4 thrombocytopenia on both OS (HR = 4.73, 95% CI = 1.95-11.52) and DFS (HR = 9.82, 95% CI = 3.14-30.76) of adult ALL, using the cohort of patients with no thrombocytopenia as a reference. In addition, treatment regimen, cytogenetic profile, time to treatment, and platelet count were independent prognostic factors of the OS. We also found that treatment regimen, cytogenetic profile, and peripheral blood blast percentage were independent prognostic factors of the DFS.

Conclusion: Grade 4 thrombocytopenia was a negative prognostic factor for both overall survival and disease-free survival of adults with acute lymphoblastic leukemia.

KEYWORDS

Acute lymphoblastic leukemia; adult; prognosis; thrombocytopenia; GMALL regimen; Hyper-CVAD regimen; pediatric regimen

Acute lymphoblastic leukemia (ALL) is a rapidly progressing hematologic cancer occurred from malignant transformations of lymphoid progenitor cells. The American Cancer Society estimated that in 2019, there would be 5,930 new ALL cases and 1,500 deaths among ALL patients in the United States of America [1]. Although the prevalence of ALL is higher in children than adults, the prognosis of adult ALL is worse than that of pediatric ALL [2,3].

Bleeding is a frequent presentation of blood malignancies, as thrombocytopenia is commonly caused by the abnormal hematopoiesis of the bone marrow [4]. Previous studies demonstrated that the pretreatment platelet count was an independent prognostic factor of overall survival (OS) in adults with certain subtypes of ALL, including Philadelphia chromosome negative ALL and B-cell ALL [5,6]. A randomized controlled trial also found that prophylactic platelet-transfusion benefitted hematologic cancer patients with grade 2 or higher bleeding [7]. However, no studies has explored the prognostic impact of the grade of thrombocytopenia on OS and disease-free survival (DFS) of adults with ALL. Therefore, we aimed to explore the prognostic impact of the grade of thrombocytopenia on both OS and DFS in adults with ALL.

Methods

This study is an extended analysis of a retrospective study conducted at the Chiang Mai University (CMU) Hospital, Chiang Mai, Thailand [8]. We retrospectively enrolled 90 newly diagnosed ALL patients aged 15–65 years at diagnosis, between January 2007 and December 2019. The enrolled patients were followed-up until 11 February 2020. According to the World Health Organization, ALL is defined as the presence of 20% or more lymphoblasts in circulation and/or bone marrow [9]. The exclusion criteria were HIV infection, incomplete complete blood count (CBC) parameters, and ineligibility of receiving intensive
chemotherapy. The decisions of chemotherapy regimen were made by patients’ physician. Since 2012, the pediatric-inspired regimen had been available for ALL patients aged 35 years or lower. The Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and the German Multicenter ALL (GMALL) regimens were also available at our institution. The details of the regimens and patient management were explained in the previous study [8]. Patients with 20,000 platelets per microliter alongside with fever or sepsis, patients with 10,000 platelets or less per microliter, and patients with any clinical bleeding received prophylactic platelet transfusion. This study was approved by the local institutional review board.

The data was collected from the database of the Division of Hematology at the CMU Hospital and the case record forms. The collected participant characteristics included age at diagnosis, gender, ALL cell types, chromosome aberration(s), presence of Philadelphia chromosome, and presence of clonal cytogenetic abnormalities (CCA). We also collected pretreatment complete blood count (CBC) parameters measured by the Automated Blood Analyser Sysmex XN 1000 and the Automated Blood Analyser Sysmex XN 9000. The CBC parameters included white blood cell count (WBC), platelet count, peripheral blood blast percentage (PBB), hemoglobin concentration (Hb), hematocrit (Hct), red blood cell distribution width (RDW), red blood cell concentration (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). The severity of thrombocytopenia was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [10]. The collected treatment outcomes included complete remission (CR), refractory, relapse, and mortality. CR, refractory, and relapse were evaluated in accordance to the WHO criteria [9].

The outcomes of this study were OS and disease-free survival DFS of the participants. The end points for OS were last follow-up date and mortality from any cause. For DFS, the end points include mortality from any cause, last follow-up date and disease relapse. We performed univariate and multivariate Cox proportional hazards regression analyses to determine the prognostic impact of the prognostic factors. The prognostic impact was evaluated by hazard ratio (HR) and 95% confidence interval (95% CI). Factors with p-value less than 0.1 will be included in the backward elimination stepwise regression. The survival curves of the OS and the DFS stratified by the grade of thrombocytopenia were generated by the Kaplan-Meier method (see supplementary file). A two tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using Microsoft Excel 2013 and the ‘survival’ package of R programming language via Rstudio version 1.2.5033 [11,12].

### Results and discussion

A total of 90 patients were included in this study (Table 1). The mean age of this included participants was 30.1 years old (range of 15–63 years old). The entire cohort consisted of 58 males and 32 females. There were 60 and 26 patients with T-cell ALL and B-cell ALL, respectively. Our cohort consisted of 17 Philadelphia chromosome positive ALL patients, accounting for the 45% of the patients with at least 1

| Characteristics                        | All patients (N = 90) |
|----------------------------------------|-----------------------|
| **Age, years; mean (range)**           | 30.1 (15–63)          |
| **Male, N (%)**                        | 58 (64.4%)            |
| **Cell type, N (%)**                   |                       |
| T-cell                                 | 26 (28.9%)            |
| B-cell                                 | 60 (66.7%)            |
| N/A                                    | 4 (4.4%)              |
| **Cytogenetic profiles, N (%)**        |                       |
| Normal, N                              | 49 (54.4%)            |
| Ph+                                    | 17 (18.9%)            |
| CCA                                    | 7 (7.8%)              |
| Ph+ with CCA                           | 5 (5.6%)              |
| Others                                 | 19 (21.1%)            |
| N/A                                    | 3 (3.3%)              |
| **Treatment protocol, N (%)**          |                       |
| Pediatric-inspired protocol            | 35 (38.9%)            |
| Adult-HCVAD                            | 39 (43.3%)            |
| Adult-GMALL                            | 16 (17.8%)            |
| **Complete blood count parameters, mean (SD)** |                   |
| RBC (×10^3/μl)                         | 3.4 (1.0)             |
| Hb (g/dl)                              | 9.2 (2.5)             |
| Hct (%)                                | 27.9 (7.6)            |
| RDW (%)                                | 17.6 (3.7)            |
| WBC (×10^3/μl)                         | 58.0 (110.0)          |
| PBB (%)                                | 41.1 (37.2)           |
| Platelets (×10^3/μl)                   | 101.4 (97.5)          |
| MCV (fl)                               | 82.6 (8.0)            |
| MCH (pg)                               | 27.2 (2.9)            |
| MCHC (g/dl)                            | 33.0 (1.6)            |
| **Thrombocytopenia, N (%)**            | 71 (78.9%)            |
| Grade 1 (Platelets 75,000–150,000 × 10^3/μl) | 23 (25.6%)           |
| Grade 2 (Platelets 50,000–75,000 × 10^3/μl) | 13 (14.4%)           |
| Grade 3 (Platelets 25,000–50,000 × 10^3/μl) | 17 (18.9%)           |
| Grade 4 (Platelets < 25,000 × 10^3/μl)  | 18 (20.0%)            |
| **Outcomes**                           |                       |
| Follow-up time, month; median (range)  | 15.7 (0.8–107.1)      |
| Time to treatment, days; median (range) | 8 (0–69)              |
| CR, N (%)                              | 74 (82.2%)            |
| Time to CR, days; median (range)       | 39.5 (1–415)          |
| Duration of continuous CR, months; median (range) | 9.2 (85.2)        |
| Alive with CR until last follow-up, N (%) | 20 (22.2%)           |
| Refractory, N (%)                      | 16 (17.8%)            |
| Relapse, N (%)                         | 43 (47.8%)            |
| Refractory or relapse, N (%)           | 59 (65.6%)            |
| Overall death, N (%)                   | 64 (71.1%)            |
| Allogenic stem cell transplantation, N (%) | 5 (5.6%)            |

CCA = clonal cytogenetic abnormalities, CG = cytogenetic profile, platelet count, CR = complete remission, GMALL = German Multicenter ALL, HCVAD = Hyper-CVAD, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, PBB = peripheral blood blast percentage, HCT = hematocrit, Hb = hemoglobin concentration, RBC = red blood cell concentration, RDW = red blood cell distribution width, WBC = white blood cell count.
Table 2. Univariate and multivariate Cox proportional hazards regression analyses of overall survival.

|                         | Univariate |        |       |
|-------------------------|------------|--------|-------|
|                         | HR  | 95% CI | p-value |
| Age                     | 1.01 | 0.99–1.03 | 0.279 |
| Gender                  | Female    | Reference |       |
|                         | Male      | 1.23   | 0.74–2.05 | 0.430 |
| Regimen                 | HCVAD     | Reference |       |
|                         | GMALL     | 4.35   | 1.11–4.35 | 0.023* |
|                         | TCP       | 1.02   | 1.00–1.36 | 0.055 |
|                         | No TCP    | 3.84   | 0.48–1.47 | 0.539 |
|                         | CCA       | Negative | Reference |
|                         | Positive  | 1.32   | 0.48–3.65 | 0.592 |
|                         | Hb        | 0.94   | 0.85–1.04 | 0.218 |
|                         | Hct       | 0.98   | 0.95–1.01 | 0.222 |
|                         | RBC       | 0.87   | 0.67–1.14 | 0.322 |
|                         | MCV       | 1.00   | 0.97–1.03 | 0.937 |
|                         | MCH       | 1.00   | 0.91–1.09 | 0.917 |
|                         | MCHC      | 1.00   | 0.86–1.16 | 0.912 |
|                         | RDW       | 0.98   | 0.92–1.04 | 0.435 |
|                         | WBC       | 1.00   | 1.00–1.00 | 0.829 |
|                         | PBB       | 1.00   | 0.99–1.00 | 0.226 |
|                         | Platelet  | 1.00   | 0.99–1.00 | 0.010* |
|                         |TCP        | No TCP | Reference |
|                         | Grade 1   | 1.11   | 0.51–2.38 | 0.793 |
|                         | Grade 2   | 1.43   | 0.62–3.31 | 0.400 |
|                         | Grade 3   | 0.91   | 0.40–2.12 | 0.835 |
|                         | Grade 4   | 2.39   | 1.09–5.23 | 0.029* |

*p < 0.05, **p < 0.01.

The grade thrombocytopenia was derived from the platelet count. Due to the high correlation, we only included the grade thrombocytopenia in the multivariate analysis.

95% CI = 95% confidence interval, CCA = clonal cytogenetic abnormalities, CG = cytogenetic profile, platelet count, GMALL = German Multicenter ALL, HCVAD = Hyper-CVAD, HR = hazard ratio, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, PBB = peripheral blood blast percentage, Ped = pediatric-inspired regimen, HCT = hematocrit, Hb = hemoglobin concentration, RBC = red blood cell concentration, RDW = red blood cell distribution width, TCP = thrombocytopenia, WBC = white blood cell count.

chromosomal abnormality. The median time from diagnosis to treatment was 8 days. Five patients received allogeneic hematopoietic stem cell transplantation. There were 71 patients with pretreatment platelet less than 150 × 10^3/µl. Of those with pretreatment thrombocytopenia, 18 of them had grade 4 pretreatment thrombocytopenia. The median follow-up duration of this cohort was 15.7 months. There were 26 patients alive and 20 patients living without ALL at the completion of follow-up period. Of the 74 patients who received CR, the disease relapsed in 59 patients.

The median OS duration was 15.7 months. Despite platelet count not being a significant predictor for OS in the univariate Cox regression (p = 0.100), grade 4 thrombocytopenia demonstrated the negative prognostic impact on OS compared with no thrombocytopenia (p = 0.029). The Kaplan Meier plot for OS was provided in the supplementary file (see Figure 1S). The multivariate Cox regression analysis of OS showed that the duration from diagnosis to treatment was a negative prognostic factor of OS (HR = 1.02, 95% CI = 1.00–1.04). Patients with normal cytogenetic had worse OS than patients with abnormal cytogenetic (HR = 2.59, 95% CI = 1.41–4.69) (Table 2).

The median DFS duration was 12.5 months. Although platelet did not show a significant prognostic impact on DFS (p = 0.010), grade 4 thrombocytopenia demonstrated the negative prognostic impact on DFS in the univariate Cox regression analysis compared with no thrombocytopenia (p = 0.049). The Kaplan Meier plot for DFS was provided in the supplementary file (see Figure 2S). The multivariate Cox regression analysis showed that grade 4 thrombocytopenia was an independent prognostic factor of DFS (HR = 9.82, 95% CI = 3.14–30.76) (Table 3).

This was the first study to demonstrate the independent prognostic impact of grade 4 thrombocytopenia on both OS and DFS of adult ALL. Although this study did not find a significant prognostic impact of pretreatment platelet count adults ALL, the results still supported the hypothesis of low platelet count being a negative prognostic factor for OS of adults with ALL [5,6]. However, other grades of thrombocytopenia did not show significant correlation with the survival of adults with ALL. From the current evidence, we proposed that the grade of thrombocytopenia reflects the severity of bone marrow failure, a condition resulted from excessive production of lymphoblast. Our study also supported the evidence that peripheral blood blast has an independent prognostic impact on OS of adult ALL [13]. Despite RDW being a negative prognostic factor in hematologic malignancies [14],
we did not find any prognostic impact of RDW on either OS or DFS in adult ALL. This finding was consistent with a study exploring the prognostic impact of RDW in children ALL [15]. Although this was a single-center retrospective extended analysis, pretreatment grade 4 thrombocytopenia was an independent negative prognostic factor of both overall survival and disease-free survival in adults with acute lymphoblastic leukemia. This study suggested the role of bone marrow failure in the prognostication of adult acute lymphoblastic leukemia. Further research studies are warranted to confirm the prognostic impact of thrombocytopenia and the underlying pathogenesis of thrombocytopenia in adult acute lymphoblastic leukemia. In addition, guidelines regarding the management of thrombocytopenia in adult acute lymphoblastic leukemia should be revised.

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Table 3. Univariate and multivariate Cox proportional hazards regression analyses of disease-free survival.

| Variable      | Univariate |                         |                         | Multivariate |                         |                         |
|---------------|------------|--------------------------|--------------------------|--------------|--------------------------|--------------------------|
| HR            | 95% CI     | p-value                  | HR                       | 95% CI       | p-value                  |
| Age           | 1.00       | 0.98–1.03                | 0.646                    | Reference    |                         |
| Gender        | Male       | 1.58                     | 0.81–3.09                | 0.182        | Reference                |
| HCVAD         | 1.96       | 0.96–3.99                | 0.063                    | 2.51         | 1.15–5.46                | 0.021*                   |
| GMALL         | 3.86       | 1.61–9.23                | 0.002**                  | 7.67         | 2.71–21.81               | <0.0001                  |
| Time to treatment | 1.01 | 0.98–1.03                | 0.522                    | Reference    |                         |
| Cell type     | B-cell     | Reference                |                         | Reference    |                         |
| Ph            | Negative   | 2.48                     | 1.24–4.99                | 0.011*       | 2.70                     | 1.27–5.74                | 0.010*                   |
| CCA           | Negative   | 0.70                     | 0.31–1.57                | 0.385        |                         |
| Hb            | 0.96       | 0.85–1.09                | 0.561                    | Reference    |                         |
| Hct           | 0.99       | 0.94–1.03                | 0.491                    | Reference    |                         |
| RBC           | 0.93       | 0.67–1.30                | 0.675                    | Reference    |                         |
| MCV           | 1.00       | 0.96–1.04                | 0.943                    | Reference    |                         |
| MCH           | 1.03       | 0.92–1.15                | 0.631                    | Reference    |                         |
| MCHC          | 1.11       | 0.91–1.36                | 0.316                    | Reference    |                         |
| RDW           | 0.93       | 0.85–1.01                | 0.069                    | Reference    |                         |
| WBC           | 1.00       | 0.99–1.00                | 0.434                    | Reference    |                         |
| PBB           | 0.99       | 0.98–1.00                | 0.006**                  | 0.99         | 0.98–1.00                | 0.009**                  |
| Platelet      | 1.00       | 1.00–1.00                | 0.294                    | Reference    |                         |
| TCP Grade 0   | 1.13       | 0.46–2.78                | 0.794                    | 1.55         | 0.57–4.26                | 0.394                    |
| TCP Grade 1   | 0.62       | 0.19–2.05                | 0.430                    | 0.75         | 0.22–2.58                | 0.767                    |
| TCP Grade 2   | 1.03       | 0.39–2.67                | 0.958                    | 2.00         | 0.73–5.63                | 0.297                    |
| TCP Grade 4   | 2.57       | 1.00–6.60                | 0.049*                   | 9.82         | 3.14–30.76               | <0.0001                  |

*p < 0.05, **p < 0.01.
95% CI = 95% confidence interval, CCA = clonal cytogenetic abnormalities, CG = cytogenetic, platelet count, GMALL = German Multicenter ALL, HCVAD = Hyper-CVAD, HR = hazard ratio, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, PBB = peripheral blood blast percentage, Ped = pediatric-inspired regimen, HCT = hematocrit, Hb = hemoglobin concentration, RBC = red blood cell concentration, RDW = red blood cell distribution width, TCP = thrombocytopenia, WBC = white blood cell count.

Disclosure statement

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
[2] Cancer Statistics Review. 1975–2013 – Previous version - SEER Cancer Statistics Review. SEER. Available from: https://seer.cancer.gov/archive/csr/1975_2013/index.html
[3] Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111:1827–1833.
[4] Shahrai S, Behzad MM, Jaseb K, et al. Thrombocytopenia in leukemia: pathogenesis and prognosis. Histol Histopathol. 2018;33:895–908.

[5] Sirop SJ, Al-Kali A, Begna K, et al. Lack of prognostic significance of monosomal karyotype and absolute lymphocyte count at diagnosis in Philadelphia chromosome negative acute lymphoblastic leukemia. Blood. 2012;120:1474–1476.

[6] Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood. 2017;129:572–581.

[7] Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med. 2013;368:1771–1780.

[8] Tantiworawit A, Rattanathammethe T, Chai-Adisaksoha C, et al. Outcomes of adult acute lymphoblastic leukemia in the era of pediatric-inspired regimens: a single-center experience. Int J Hematol 2019;110:295–305.

[9] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391–2405.

[10] Common Terminology Criteria for Adverse Events (CTCAE). Protocol development. CTEP; Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[11] Therneau T. A package for survival analysis in R. R package version 3.1–11.

[12] RStudio Team. RStudio: integrated development for R. Boston (MA): RStudio, Inc.; 2019.

[13] Amin HM, Yang Y, Shen Y, et al. Having a higher blast percentage in circulation than bone marrow: clinical implications in myelodysplastic syndrome and acute lymphoid and myeloid leukemias. Leukemia. 2005;19:1567–1572.

[14] Ai L, Mu S, Hu Y. Prognostic role of RDW in hematological malignancies: a systematic review and meta-analysis. Cancer Cell Int. 2018;18:61.

[15] Rafsanjani KA, Falahati V, Kiumarsi A, et al. The association between red cell distribution width and mortality in pediatric acute lymphoblastic leukemia. J Neoplasm. 2017;2:1–3.