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ORIGINAL ARTICLE

Usefulness of two clinical (CBC and PETHEMA) scores for predicting early death in patients with acute promyelocytic leukemia: A single-center study in Mexico City

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Abstract

Background: *The use of all-transretinoic acid together with chemotherapy has improved the prognosis of patients with acute promyelocytic leukemia (APL). However, less than 20% still die prematurely, mainly from hemorrhage.* **Objective:** *The objective of this study was to identify the utility of the PETHEMA score and complete blood count (CBC) score for the detection of patients with APL at risk of premature death.* **Materials and methods:** *A retrospective observational study in patients with de novo APL treated between 2001 and 2015 at Hospital General de México.* **Results:** *Among the 79 patients studied, the mean age was 35 years (17-57 years). According to the PETHEMA score, most patients were deemed low risk (n = 34, 42.5%) followed by high-risk (n = 25, 31%) and intermediate-risk patients (n = 21, 26.3%). As per the CBC score, 16.3% (n = 13), 31.3% (n = 25) and 52.5% of patients (n = 42) were considered as low-risk (0 points), intermediate-risk (1 and 2 points), and high-risk patients, respectively (3 points). Overall survival at 5 years was 73%, with a lower rate in those patients considered as high risk for the two scales. Individually, both thrombocytopenia and elevated fibrinogen levels were associated with premature death.* **Conclusion:** *The PETHEMA score, like the CBC score, allows for the identification of patients at risk of premature death, with as thrombocytopenia is an independent risk factor.*

Key words: *Acute promyelocytic leukemia. Survival analysis. Prognosis.*

Introduction

Acute promyelocytic leukemia (APL) is a neoplasm characterized by the blockage of myeloid cell differentiation mainly secondary to t(15; 17) (q24.1; q21.2)[1]. Its prevalence is high in Latin America and the Caribbean[2]. Studies conducted in the United States (California and Florida) have identified that its frequency is higher in the Latino population compared to Anglo-Saxons (24.3% vs. 8.3%) or even African-Americans[3,4]. Unlike other types of leukemia, treatment is highly effective and based on the use of all-transretinoic acid (ATRA) which allows for the differentiation of promyelocytes to granulocytes[5,6]. Various cooperative groups worldwide (PETHEMA,

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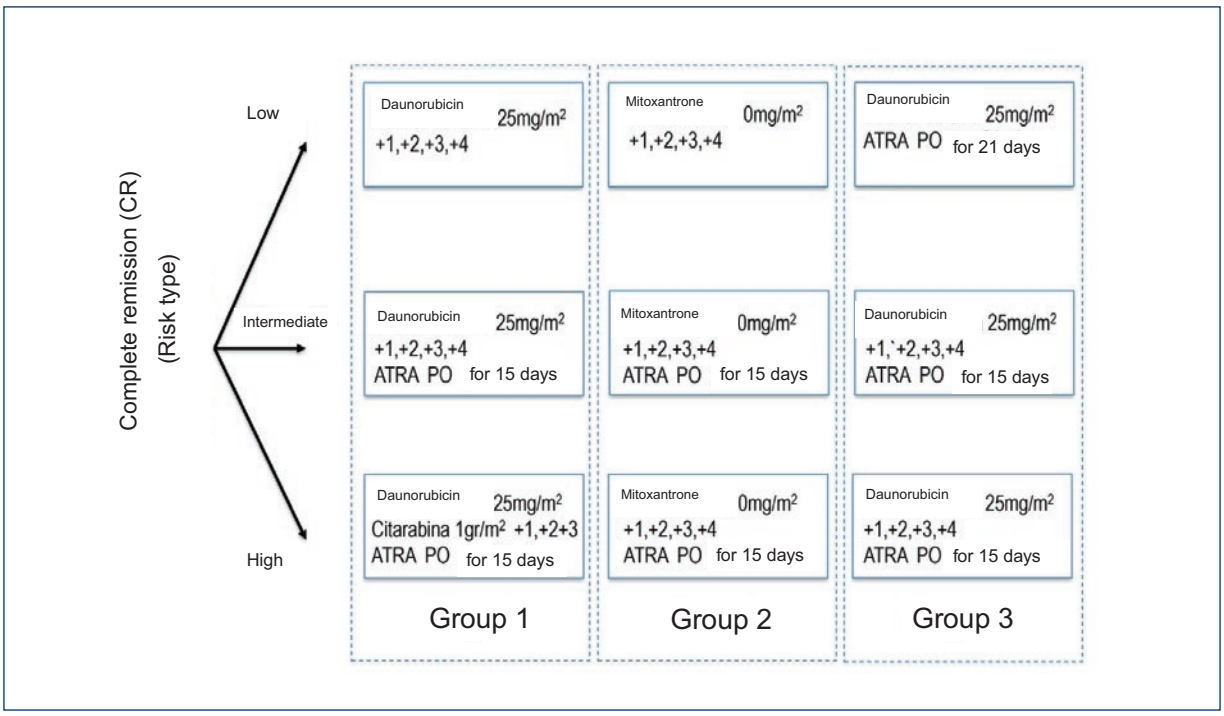

Figure 1. Risk-based consolidation scheme, the risk was established according to the PETHEMA score.

GIMEMA, and HOVON) have identified that the most effective combination during induction is with some type of anthracycline (Daunorubicin [DAU] or Idarubicin) and more recently with arsenic trioxide (ATO)[7-11]. For Latin America, the International Consortium on APL (IC-APL) recommends the use of DAU mainly due to its easy access and safety profile[12]. Recently, Crespo-Solis et al. published the experience of using an adaptation of the IC-APL guidelines, in a health center in Mexico City, reaching a 94.4% complete remission (CR) rate and 89.1% overall survival rate[13]. Despite the high response rate, less than 20% of patients die prematurely, mostly due to hemorrhages[14]. Unfortunately, mortality is still high, especially in countries with poor access to ATRA and in patients considered as high-risk patients[15-17]. This risk (low, intermediate, and high) is established using the classification of the Spanish group PETHEMA (Spanish Program on Hematology Treatments) which is based on the combination of two variables; leukocyte count and platelet count, considering those cases with values above 10 × 10^9/L leukocytes such as high-risk patients[18,19]. An increasing number of factors have been assimilated to identify high-risk patients. The main ones are at the molecular level (FLT3-ITD mutation) and flow cytometry (CD56, CD2, and CD34)[20,21]. To improve the clinical scale, Park et al. included hemoglobin values into the risk score, known as complete blood count (CBC) score, and unlike the PETHEMA score, the risk was established with the sum of each of the different values[22]. The main objective of this study was to identify the utility of the two scales (PETHEMA and CBC score) on the risk of premature death of patients with APL undergoing an ATRA and DAU-based treatment as induction therapy.

Materials and methods

Study design

A retrospective, observational study in patients diagnosed with *de novo* APL treated at the Hematology Department of *Hospital General de México* from January 2001 to June 2015.

Treatment protocol

Induction

ATRA was administered for 45 days at a dose of 10 mg/10 kg of body weight, together with DAU at a dose of 45 mg/m² of body surface area on days +2, +4, +6, and +8.

Consolidation

Three monthly blocks were used, according to the type of risk. ATRA was added to the treatment of intermediate- or high-risk patients. The consolidation scheme is described in figure 1.

Maintenance

Maintenance lasted for 2 years, based on 6-mercaptopurine at a dose of 50 mg/m² administered orally on a daily basis and 50 mg intramuscular methotrexate on a weekly basis. Administration of ATRA took place every 3 months for a period of 15 days.

Dexamethasone 8 mg was added preventively to the treatment of high-risk patients 3 times a day. In case of suspicion of differentiation syndrome, ATRA administration was suspended until improvement of symptoms.

Risk scales

Under the PETHEMA classification, high risk was considered: leukocytes ≥ 10 × 10^9/L; intermediate risk: leukocytes < 10 × 10^9/L and/or platelets ≤ 40 × 10^9/L; and low risk if leukocytes < 10 × 10^9/L and/or platelets > 40 × 10^9/L[18,19].

The CBC scoring system assigns 1 point to each variable: leukocytes ≥ 10 × 10^9/L, platelets ≤ 40 × 10^9/L, hemoglobin ≤ 8 g/dL; and the level of risk is due to the sum of points: low (0 points), intermediate (1 point), and high (2-3 points).

Statistical analysis

Data were analyzed with IBM SPSS statistical software, version 20.0. For the analysis of the prognostic impact of the scores as well as the different variables on mortality, a multivariate analysis was performed, identifying the risk (OR) for each risk variable. Survival curves were obtained by the Kaplan–Meier method. The results whose hypothesis contrast test yielded p ≤ 0.05 were deemed statistically significant.

Ethical considerations

All patients were provided with informed consent by the institution for the administration of treatment as well as for the administration of transfusion support.

Results

From January 2001 to June 2015, 82 patients with APL were analyzed and included in the institutional protocol, HGMLAP-2001. Only three cases were excluded, due to the lack of information for the final analysis. ATRA administration was initiated early in all patients accompanied by transfusion support.

Table 1. Qualitative features of patients with APL treated at *Hospital General de México* between 2001 and 2015

Feature	n (%)
Total patients	79
Gender	
Males	33 (41.8)
Females	46 (58.2)
Clinical manifestations	
ATRA syndrome	12 (15.2)
Febrile neutropenia	50 (63.3)
Mild hemorrhage	27 (34.2)
Moderate-severe hemorrhage	48 (60.8)
Central nervous system hemorrhage	4 (5.1)
PETHEMA score	
Low risk	19 (24.1)
Intermediate risk	36 (45.6)
High risk	24 (30.4)
CBC score	
Low risk (0 points)	12 (15.2)
Intermediate risk (1 point)	27 (34.2)
High risk (2 and 3 points)	40 (50.6)

APL: acute promyelocytic leukemia; CBC: complete blood count.

Patient's characteristics

Among the 79 eligible patients, 58.2% were female (n = 46); the average age was 34 years (range 17-57 years). Only 10% of patients were older than 50 years at the time of diagnosis.

The mean white blood cell count at diagnosis was 14.54 × 10^9/L (range 0.38-204 × 10^9/L), but the majority were with < 10 × 10^9/L (69.6%), 11.3% of the cases showed values above 50 × 10^9/L at the time of diagnosis. The mean platelet volume was 39.21 × 10^9/L (range 4-272 × 10^9/L); being mostly < 50 × 10^9/L (73.8%).

The main clinical manifestation at diagnosis was hemorrhage followed by anemic syndrome. No splenomegaly or nodal growth was documented in any patient. Among the 80 eligible cases, only 3.8% (n = 3) presented a creatinine value above 1.5 mg/dL at diagnosis and 7.5% (n = 6) presented bilirubin levels > 2 mg/dL isolated or in conjunction with elevated aspartate aminotransferase or alanine transaminase levels.

The qualitative and quantitative features of the studied population are described in tables 1 and 2, respectively.

Classification according to risk

Table 1 shows the number of patients classified in each risk level according to the PETHEMA scales and CBC score.

Table 2. Quantitative features of patients with APL treated at *Hospital General de México* between 2001 and 2015

Analyte	Mean (range)	Standard deviation
Age (range)	34 (17-57)	± 11.8
Leukocytes (×10^9/L) n cases with < 10 (%) n cases with ≥ 10 (%)	14.54 (0.38-204) 55 (69.6) 24 (30.4)	± 30.18
Hemoglobin (g/dL) n cases with ≤ 8 (%) n cases with > 8 (%)	8.79 (3.3-17.9) 51 (64.6) 28 (35.4)	± 2.8
Platelets (×10^9/L) n cases with ≤ 40 (%) n cases with > 40 (%)	39.21 (4-272) 54 (68.4) 25 (31.6)	± 47.15
Albumin (g/dL)	3.5 (1.8-5.1)	± 0.6
AST (UI/L)	33.8 (10-141)	± 25.6
ALT (UI/L)	35.1 (10-117)	± 24.6
Alkaline phosphatase (UI/L)	88.7 (35-371)	± 52.4
Lactate dehydrogenase (UI/L)	327 (100-1272)	± 211.5
Bilirubin (mg/dL)	0.99 (0.32-5.4)	± 0.72
Creatinine (mg/dL)	0.79 (0.3-1.6)	± 0.25
Urea (mg/dL)	30.05 (6.4-76.3)	± 13.09
PT (s)	14.9 (11.3-25.9)	± 2.7
aPTT (s)	26.3 (18.2-49.8)	± 4.9
TT (s)	22.4 (12-117)	± 13.7
Fibrinogen (g/dL)	227.1 (0-671)	± 129.6

PT: prothrombin time; aPPT: activated partial thromboplastin time; TT: thrombin time; APL: acute promyelocytic leukemia; ALT: alanine transaminase; AST: aspartate aminotransferase.

Treatment response

The rate of CRs was 74.7% of cases (n = 59), with a therapeutic failure of 25.3% of cases (n = 20). During induction therapy, 62.5% of patients (n = 50) developed febrile neutropenia, with 16% of patients (n = 8) dying from sepsis.

The differentiation syndrome was perceived in 15% of patients (n = 12), with 3 patients (3.8%) dying from this complication.

Survival

At a mean follow-up of 2.8 years (112 days-13.4 years), the overall survival rate was 76%. The overall mortality rate was 25.3% (n = 21). When analyzing the survival rate according to each of the risk groups, the patients considered as low risk by the PETHEMA scale showed a higher survival rate (86%) compared to those high-risk patients (58%). When analyzing the survival rate according to the CBC score, patients without any risk score showed a higher survival rate (92%), unlike those patients who scored different risk factors (60% in those patients with three points). Survival according to each of the PETHEMA and CBC risk groups is described in figure 2.

Factors associated with mortality

Individually, severe thrombocytopenia (< 40 × 10^9/L) as well as prolonged thrombin time behaved as a risk factor for death, but elevated serum fibrinogen levels also behaved as an independent risk factor for premature and late death. Both PETHEMA and CBC scores behaved as a global risk factor, but the latter allowed patients to be better distinguished. Table 3 describes the risk value of the different variables for both premature and late death.

Association between CBC and PETHEMA score

When analyzing the risk groups, most patients were in the intermediate-risk group (n = 36, 45.6%) followed by the high-risk group (n = 24, 30.4%) in the PETHEMA score. However, when searching for the correlation between the two scales, the patients considered as low or high risk for the PETHEMA score had 0-3 factors for the CBC score, respectively. A greater discrepancy was registered in those patients who had between one and two risk factors, as they were distributed between the intermediate- and high-risk group of the PETHEMA score, respectively.

Discussion and conclusions

APL is a major hematological emergency, due to its high risk of death at the time of diagnosis due to a hemorrhagic event. Early administration of ATRA together with intensive transfusion support is the main strategies for reducing mortality[23]. Mortality associated with leukemia was lower compared to our historical record, mainly occurring in high-risk patients.

When comparing the two scales, similarity was only identified in the low-risk groups (low-risk PETHEMA or patients with zero CBC score, that is, without relevant biochemical alterations) as cases were identified in the group of intermediate-risk patients with

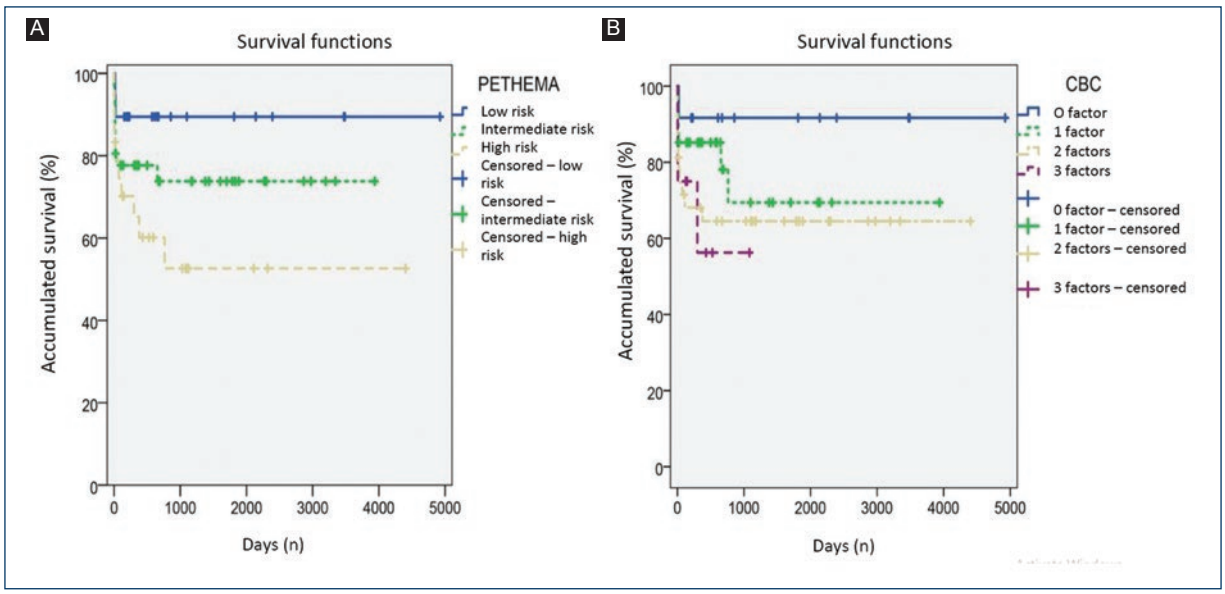

Figure 2. Overall survival of patients with acute promyelocytic leukemia according to the risk group; **A:** PETHEMA score; **B:** complete blood count score.

Table 3. Risk value for premature and late death of the different variables

Variable	Risk group	p value	Mortality OR (confidence interval at 95%)	30-day mortality OR (confidence interval at 95%)
Hemoglobin	< 8 g/dL	0.0739	2.5731 (0.9127-7.2543)	0.8425 (0.2819-2.5177)
Leukocytes	> 10 × 10^9/L	0.2822	0.5581 (0.1928-1.6157)	1.3333 (0.4282-4.1519)
Platelets	< 40 × 10^9/L	0.0747	3.3694 (0.8858-12.8167)	0.6007 (0.1742-2.0717)
TT	> 27 s	0.0352*	3.3629 (1.0939-12.1316)	1.4074 (0.4775-4.1478)
PT	> 14 s	0.1583	2.2588 (0.7282-7.0067)	1.5158 (0.4744-4.8436)
aPTT	> 26 s	0.6372	1.5652 (0.3947-6.2063)	2.3765 (0.7799-7.2420)
Fibrinogen	> 350 g/dL	0.0130*	3.8077 (1.3250-10.921)	3.5250 (1.1550-10.7577)
PETHEMA score	High risk	0.053	7.7727 (0.9668-62.4879)	2.8333 (0.5851-13.7203)
CBC score	High risk (2-3 points)	0.113	10.1485 (0.5737-179.5231)	3.4510 (0.4131-28.8311)

*Considering $p \leq 0.05$ as statistically significant.
PT: prothrombin time; aPPT: activated partial thromboplastin time; TT: thrombin time; CBC: complete blood count.

scores 1 and 2 in the CBC scale. The upper section of table 2 is extremely important to understand this point: two-thirds of the analyzed population (64.6%) had hemoglobin values below the cutoff point for the CBC scale; thus, placing this majority at least at intermediate risk. By integrating leukocyte and platelet values, this score is increased, which explains that for the CBC score, half of the patients had a high risk (50.6%), while only one-third of patients were at high risk (30.4%) in the PETHEMA score, as the latter scale considers only the leukocyte count alone to stratify patients as high risk.

These findings are similar to those presented by Loglisci et al. when reclassifying cases according to the CBC score. Among the cases identified as intermediate and high risk (n = 66 and n = 33), while reclassifying them according to the CBC score, most patients were identified as high-risk score 1 (n = 60) and score 2-3 (n = 47)[24]. When analyzing the different factors individually, thrombocytopenia severity was associated with mortality (OR 3.369, p = 0.07) as expected. This finding is similar to other series, in which the platelet count at the time of diagnosis is a determinant for hemorrhagic complications during the first

4 weeks of diagnosis[25]. Another risk factor that was identified for death was the level of fibrinogen. Recently, Hassan et al. identified that low levels of fibrinogen (< 1.5 g/L) were associated with a high risk of premature death[26-28]. These, in conjunction with prolonged hemostasis, are other factors to be considered at the time of diagnosis, especially on suspicions of a disseminated intravascular coagulation (DIC). Hence, Mitrovic et al. evaluated the usefulness of incorporating the score of the International Society on Thrombosis and Haemostasis for DIC (ISTH DC) to predict death associated with hemorrhage in 56 patients with APL[29]. Among the main factors were the leukocyte count (> 20 × 10^9/L), the performance status using the Eastern Cooperative Oncology Group (ECOG) score > 3, the level of fibrinogen (< 2 g/L), prothrombin time < 50%, and ISTH DC score > 6.29. So far, few trials have shown that elevated fibrinogen levels also affect mortality. In this research, a value of 350 mg/dL was associated with an increased risk of premature death (OR 3.525, p = 0.013). These data are similar to those reported by Wei et al., in which the presence of an elevated level of fibrinogen (> 400 mg/dL) was associated with an adverse prognosis in different hematological malignancies including APL[30]. Conversely, Mantha et al. analyzed several factors that were associated with premature death in five clinical trials that included the use of ATRA during induction. Among the 995 cases analyzed, both performance status and leukocyte count > 20 × 10^9/L were the major factors associated with premature death[31].

Finally, risk stratification is also useful for identifying the efficacy of new drugs. Although the combination of ATRA with chemotherapy is still the standard treatment, the use of ATRA-ATO is especially effective in patients with low/intermediate risk[32], dramatically improving hemostatic disorders[33-35]. However, unlike trials with ATRA, creatinine as well as performance status (ECOG) are the main factors of premature death associated with the use of ATO[36].

In conclusion, the use of scores such as the CBC or PETHEMA together with individual factors, such as thrombocytopenia, allows identifying those patients with APL at risk of premature death.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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