**Hematological Oncology**
*Hematol Oncol* 2017; **35**: 789–796
Published online 15 June 2016 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2307

**Original Research Article**

# Increased fibrinogen levels at diagnosis are associated with adverse outcome in patients with acute myeloid leukemia

Martin D. Berger[1], Alexander D. Heini[1], Katja Seipel[2], Beatrice Mueller[2], Anne Angelillo-Scherrer[3] and Thomas Pabst[1]*

[1]*Department of Medical Oncology, University Hospital and University of Berne, Berne, Switzerland*
[2]*Department of Clinical Research, University Hospital and University of Berne, Berne, Switzerland*
[3]*Department of Hematology, University Hospital and University of Berne, Berne, Switzerland*

**Correspondence to: Thomas Pabst, Department of Medical Oncology, University Hospital, 3010 Berne, Switzerland. E-mail: thomas.pabst@insel.ch*

*Contract/grant sponsor: EMPIRIS Stiftung.*

Received 10 February 2016
Revised 11 April 2016
Accepted 21 April 2016

## Abstract

**Increased plasma fibrinogen levels are associated with shortened overall survival (OS) in some solid tumor types. In contrast, the prognostic significance of varying fibrinogen levels in acute myeloid leukemia (AML) at diagnosis is unknown. In this study, we assessed the prognostic significance of fibrinogen levels in AML patients. In a comprehensive retrospective single-center study, we determined the survival rates of 375 consecutive AML patients undergoing at least one cycle of intensive chemotherapy induction treatment. Patients were dichotomized between low (<4.1 g/L) and high fibrinogen levels (≥4.1 g/L) at diagnosis of AML before initiation of treatment. Subsequently, quartile ranges were applied to analyze the association of varying fibrinogen levels on survival. We observed that the rates of complete remission, early death, and admission to intensive care unit were equal in the low versus high fibrinogen group. However, OS was significantly better in the low fibrinogen group (27.3 vs 13.5 months; $p = 0.0009$) as well as progression-free survival (12.3 vs 7.8 months; $p = 0.0076$). This survival difference remained significant in the multivariate analysis ($p = 0.003$). Assessing quartiles of fibrinogen values, we further confirmed this observation. Our data suggest that high fibrinogen levels at diagnosis of AML are associated with unfavorable OS and progression-free survival but not with increased mortality during induction treatment.** 

**Keywords:** **fibrinogen; AML; prognostic; biomarker; survival**

## Introduction

Fibrinogen exerts key roles in hemostasis as a substrate for fibrin clot formation and by binding to platelets to trigger platelet aggregation. In addition, fibrinogen acts as an acute phase protein and is characteristically elevated during inflammation processes [1]. Fibrinogen mainly circulates in the plasma and is composed of six polypeptide chains. It is synthesized in the liver and has a median half-life of 3 to 5 days [2,3]. High fibrinogen levels have been reported to be associated with increased risk of cardiovascular disease and mortality in tumor patients [4]. Various interactions between tumor cells and coagulation factors have been postulated, but the mechanisms involved in the association between hyperfibrinogenemia and adverse survival ultimately remain to be elucidated [5].

Whereas several reports indicated an association between elevated fibrinogen levels and shortened survival in patients with carcinoma [6–8], hypofibrinogenemia is considered not to adversely affect overall survival (OS) and disease-free survival in solid tumor patients [9]. In leukemias, low fibrinogen levels are commonly observed in patients with acute promyelocytic leukemia (APL), usually indicating activated disseminated intravasal coagulation (DIC) [10]. However, the prognostic significance of varying plasma fibrinogen levels in patients with acute myeloid leukemia (AML) has not been reported.

Currently used risk classification in AML is predominantly based on cytogenetic and molecular abnormalities and response to treatment [11]. Clinical parameters including age, lactate dehydrogenase (LDH), or leukocyte counts may further provide specific prognostic information [11]. In this study, we tested the hypothesis whether varying fibrinogen levels at diagnosis of AML confer specific prognostic information in AML patients undergoing intensive chemotherapy.

## Methods

### Patients

Between 1984 and 2014, all patients diagnosed with AML at the University Hospital of Bern, Switzerland, were

included in this analysis. The study was approved by the local ethics committee of Bern, Switzerland (decision number 232/2014). We limited our analysis to newly diagnosed AML patients effectively receiving at least one cycle of intensive chemotherapy. Patients were stratified into two groups with high (≥4.10 g/L) versus low (normal) fibrinogen (<4.10 g/L) plasma levels at diagnosis. Data were collected on gender, age at diagnosis, hemoglobin, white blood cell count, platelets, peripheral and marrow blasts, LDH, D-dimers, prothrombin time, and the International Society for Thrombosis and Hemostasis (ISTH) DIC score [12] at diagnosis. The French–American–British (FAB) classification [13] for patients diagnosed between 1984 and 1999 and, subsequently, the WHO classification versions 1999 [14], 2001 [15], and 2008 [16] were used.

Patients were consistently treated within or according to the following protocols of the Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON)–Swiss Group for Clinical Cancer Research (SAKK): HOVON-29, HOVON-42, HOVON-43, HOVON-81, HOVON-92, HOVON-102, and HOVON-103; or the French/SAKK APL protocols APL-93, APL-2000, and APL-2005. Induction chemotherapy consisted of two cycles with cytarabine/idarubicin (cycle 1) and cytarabine/amsacrin (cycle 2). Consolidation therapy consisted either of a third cycle of chemotherapy (with mitoxantrone and etoposide) or of high-dose chemotherapy (with busulfan and cyclophosphamide) followed by autologous stem cell transplantation for patients with good or intermediate risk profile or of allogeneic stem cell transplantation for patients with adverse risk profile.

Patients were eligible if they were at least 18 years old, not pregnant or lactating, and following reliable birth control methods. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, were without other active malignancies, and did not receive preceding treatment for AML with the exception of hydroxyurea.

### Measurements and definitions

Response criteria were assessed according to the guidelines of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in AML [17]. Bone marrow examinations were performed on day 18 and 28 of each cycle. Complete remission (CR) was defined as a bone marrow blast count of <5% with a concomitant absolute neutrophil count of $>1.0\times10^9$/L for 3 consecutive days and a platelet count above 100 g/L without transfusions in the 3 previous days. Complete remission with incomplete hematologic recovery (CRi) was defined as a bone marrow blast count of <5% with an absolute neutrophil count of $<1.0\times10^9$/L or a platelet count of <100 g/L. Fibrinogen measurements were performed according to the Clauss method.

### Statistical analysis

Overall survival was defined as the time from initiation of therapy at diagnosis until death from any cause or last follow-up. Patients still alive or lost to follow-up were censored at the last date when they were known to be alive. Progression-free survival (PFS) was defined as time from initiation of therapy at diagnosis until relapse or death or until last follow-up in patients with ongoing remission or as time from diagnosis until death, assessment of refractoriness, or last follow-up in patients not being in (CRi) before. Non-relapsing patients were censored at the last date of follow up. Patients with a blast count of >5% in the bone marrow on day 28 after the second induction therapy were defined as refractory.

Curves depicting OS and disease-free survival were calculated using the Kaplan–Meier method. Survival analysis was performed using the log-rank method. Hazard ratios to evaluate the impact of baseline characteristics on clinical outcome were calculated using the log-rank method. To adjust for factors associated with outcome, we performed a multivariate Cox proportional hazard regression model. Fibrinogen and other non-binary variables were used as continuous variables in the multivariate analysis.

All $p$-values were from two-tailed Mann–Whitney or unpaired $t$ tests, and a value of $p < 0.05$ was considered to be statistically significant. Statistical analysis was conducted using GraphPad Prism version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA) and R version 3.7.7. (R Foundation, Vienna, Austria).

## Results

The study comprised 375 consecutive patients with AML at diagnosis receiving at least one cycle of standard induction chemotherapy. Subsequent consolidation therapy was conducted in the low versus high fibrinogen group either with chemotherapy alone (30.2% vs 25.0%, $p=0.4147$), with high-dose chemotherapy followed by autologous stem cell transplantation (29.6% vs 37.1%, $p=0.1961$), or with allogeneic hematopoietic stem cell transplantation (22.0% vs 12.9%, $p=0.0587$) according to their individual risk profile and ECOG performance status. About 88.2% of the patients were treated within a study protocol. Baseline characteristics of the low and high fibrinogen cohorts are summarized in Table 1.

The median age of the patients, white blood cell counts, platelets, peripheral and marrow blasts, and LDH values were equally distributed in the high versus low fibrinogen groups. In contrast, hemoglobin levels at diagnosis ($p=0.0069$) and the ISTH DIC scores ($p=0.0151$) were higher in the low



DOI: 10.1002/hon

**Table 1**. Patient characteristics at diagnosis according to pre-treatment fibrinogen plasma levels

| | Fibrinogen <4.10 g/L (*n* = 214) | Fibrinogen ≥4.10 g/L (*n* = 161) | all (*n* = 375) | *p* |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Age (range) | 52.8 (16.6–76.6) | 54.4 (18.5–75.4) | 54.1 (16.6–76.6) | 0.3689 |
| Female/male (%) | 107/107 (50/50) | 58/103 (36/64) | 165/210 (44/56) | 0.0085 |
| Hemoglobin (g/L) | 93.0 (9.3–167.0) | 88.0 (1.3–155.0) | 91.0 (1.3–167.0) | 0.0069 |
| WBC (G/L) | 8.9 (0.5–388.5) | 10.6 (0.6–360.5) | 10.1 (0.5–388.5) | 0.8863 |
| Peripheral blasts (%) | 33.8 (0–96.0) | 39.0 (0–99.0) | 38.0 (0–99.0) | 0.1326 |
| Marrow blasts (%) | 75.0 (0–95.0) | 70.0 (0–95.0) | 70.0 (0–95.0) | 0.0954 |
| Platelets (g/L) | 61.0 (4.0–409.0) | 62.0 (5.0–522.0) | 61 (4.0–522.0) | 0.8136 |
| Fibrinogen (g/L) | 2.97 (0.15–4.05) | 5.60 (4.19–8.80) | 3.79 (0.15–8.80) | – |
| CRP (mg/L) | 8.0 (1.0–348.0) | 61 (3.0–438.0) | 20.0 (1.0–438.0) | <0.0001 |
| LDH (IU/L) | 733.5 (156–18 856) | 728 (171–5813) | 728 (156–18'856) | 0.9643 |
| ISTH DIC Score | 4 (0–8) | 3 (0–7) | 4 (0–8) | 0.0151 |
| FAB classification (%) | | | | |
| Biphenotypic | 1 (0.5) | 0 (0.0) | 1 (0.2) | 1.0000 |
| M0/M1 | 52 (24.3) | 62 (38.5) | 114 (30.4) | 0.0033 |
| M2 | 46 (21.5) | 42 (26.1) | 88 (23.5) | 0.3257 |
| M3 | 30 (14.0) | 1 (0.6) | 31 (8.3) | <0.0001 |
| M4 | 30 (14.0) | 22 (13.7) | 52 (13.9) | 1.0000 |
| M5 | 25 (11.7) | 11 (6.8) | 36 (9.6) | 0.1559 |
| M6 | 8 (3.7) | 4 (2.5) | 12 (3.2) | 0.5662 |
| M7 | 2 (0.9) | 6 (3.7%) | 8 (2.1) | 0.0790 |
| Undefined | 20 (9.4) | 13 (8.1) | 33 (8.8) | 0.7159 |
| *De novo*/secondary AML | | | | |
| *De novo* AML | 177 (82.7) | 124 (77.0) | 301 (80.3) | 0.1907 |
| Secondary AML | 37 (17.3) | 37 (22.9) | 74 (19.7) | 0.1907 |
| Risk classification | | | | |
| Favorable | 61 (28.5) | 32 (19.9) | 93 (24.8) | 0.0697 |
| Without *t*(15;17) | 31 (14.5) | 31 (19.3) | 62 (16.5) | 0.2613 |
| *t*(15;17) | 30 (14.0) | 1 (0.6) | 31 (8.3) | <0.0001 |
| Intermediate | 119 (55.6) | 90 (55.9) | 209 (55.7) | 1.0000 |
| Adverse | 34 (15.9) | 39 (24.2) | 73 (19.5) | 0.0486 |
| Consolidation in CR1[1] | | | | |
| Allogeneic transplant | 35 (22.0) | 15 (12.9) | 50 (18.2) | 0.0587 |
| Autologous transplant | 47 (29.6) | 43 (37.1) | 90 (32.7) | 0.1961 |
| Allogeneic after autologous transplant | 8 (5.0) | 6 (5.2) | 14 (5.1) | 1.0000 |
| Chemotherapy | 48 (30.2) | 29 (25.0) | 77 (28.0) | 0.4147 |
| No consolidation | 21 (13.2) | 23 (19.8) | 44 (16.0) | 0.1823 |
| Follow-up (months) | 84.1 | 70.8 | 79.0 | 0.0966 |

WBC, white blood cells; CR1, first complete remission; CRP, C-reactive protein; ISTH DIC, International Society for Thrombosis and Hemostasis disseminated intravasal coagulation; FAB, French–American–British; AML, acute myeloid leukemia.
Median values are indicated wherever not otherwise indicated.
[1]Percentages of patients who achieved CR.

fibrinogen group. The various AML subtypes according to the FAB classification (M0–M7) were equally distributed in both cohorts, except for AML-M3/APL ($p = 0.0001$), which were more frequently observed in the low fibrinogen group, and for AML with FAB types M0/M1, which were more often found in the high fibrinogen group ($p = 0.0033$). Also, more patients with *t*(8;21) were seen in the high fibrinogen group (9.3% vs 1.9%) ($p = 0.0015$). Levels of C-reactive protein at diagnosis closely correlated with fibrinogen levels (Spearman's coefficient $\rho = 0.55$; $p < 0.001$). Furthermore, higher fibrinogen levels were associated with lower D-dimer levels ($p = 0.0014$), lower international normalized ratio ($p = 0.0001$), and male gender ($p = 0.0030$), whereas low fibrinogen values correlated with female gender ($p = 0.0030$). The median follow-up was 84.1 (range 0.1 to 233.1) months in the low fibrinogen group and 70.8 (0.1 to 161.3) months in the high fibrinogen group ($p = 0.0966$).

Significant differences were observed in the survival rates (Figure 1). The median OS was 27.3 months in the low fibrinogen group and 13.5 months in the high fibrinogen group ($p = 0.0009$). Also, the median PFS was better in the low fibrinogen group (12.3 months) compared with the high fibrinogen group (7.8 months; $p = 0.0076$).

When limiting the analysis to non-APL patients, we found that the low fibrinogen group ($n = 184$) still had a better median OS compared with the high fibrinogen group



DOI: 10.1002/hon

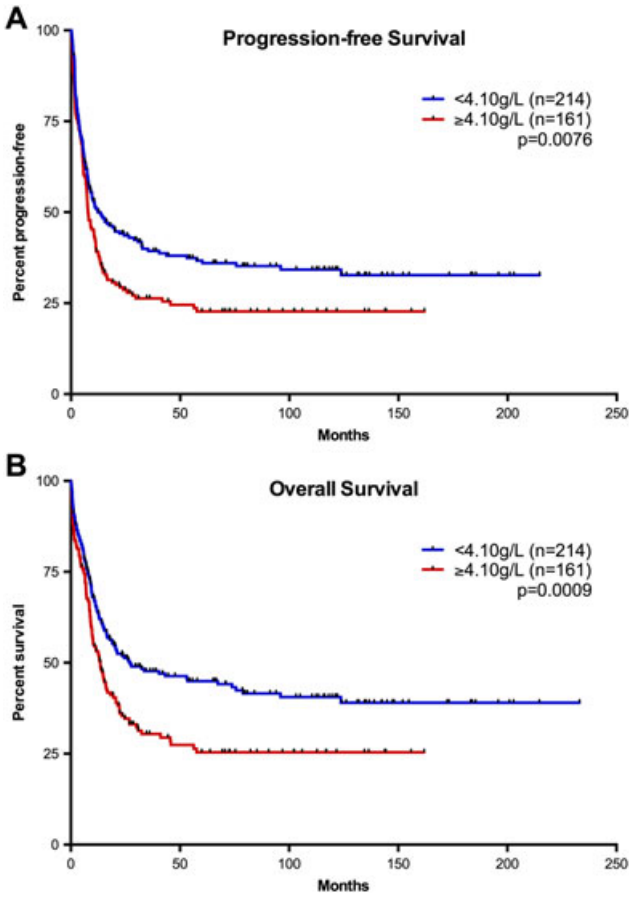


**Figure 1.** Kaplan–Meier curves are presented for progression-free survival (panel **A**) and overall survival (panel **B**).

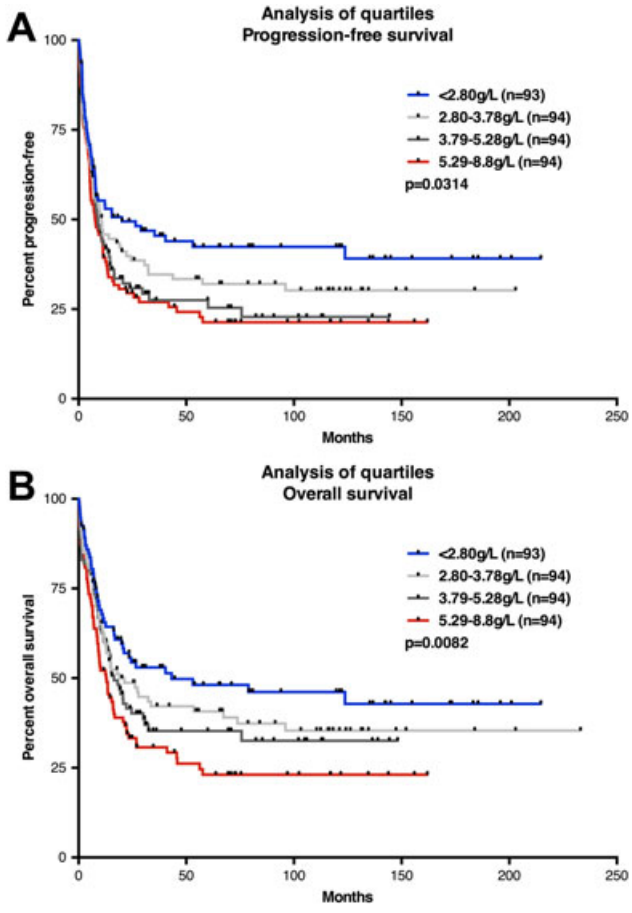


**Figure 2.** Kaplan–Meier curves representing overall survival according to quartiles of fibrinogen plasma levels for progression-free survival (panel **A**) and overall survival (panel **B**).

($n = 160$) with 20.6 versus 13.5 months ($p = 0.0097$). In addition, Figure 2 shows survival curves according to the quartiles of fibrinogen plasma levels (low to high quartile) to better analyze the association of increased fibrinogen levels with worse survival outcomes. No differences in the complete (CR) and incomplete (CRi) remission rates (74.3% vs 72.0%, $p = 0.6387$ and 8.4% vs 6.2%, $p = 0.5523$, respectively) were detected between the two groups (Table 2 and Table S2). In addition, early mortality until 30 days (7% vs 11.8%, $p = 0.1453$) and until 100 days (15.4% vs 18.6%, $p = 0.4856$) as well as intensive care unit (ICU) admission rates (35% vs 37.9%, $p = 0.5888$) were similar in the low and high fibrinogen groups. As outlined in Table S1, patients with a normal karyotype showed no significant differences in

**Table 2.** Survival, response, early mortality, and ICU admission rates according to pre-treatment fibrinogen levels

| | Fibrinogen <4.10 g/L ($n = 214$) (%) | Fibrinogen ≥4.10 g/L ($n = 161$) (%) | All ($n = 375$) (%) | *p* |
|---|---|---|---|---|
| OS (months; median) | 27.30 | 13.47 | 17.87 | 0.0009 |
| PFS (months; median) | 12.30 | 7.83 | 9.83 | 0.0076 |
| CRi | 18 (8.4) | 10 (6.2) | 28 (7.5) | 0.5523 |
| CR | 159 (74.3) | 116 (72.0) | 275 (73.3) | 0.6387 |
| CR + CRi | 177 (82.7) | 126 (78.3) | 303 (80.8) | 0.2918 |
| Early mortality 30 days | 15 (7.0) | 19 (11.8) | 34 (9.1) | 0.1453 |
| Early mortality 100 days | 33 (15.4) | 30 (18.6) | 63 (16.8) | 0.4856 |
| ICU admission | 75 (35.0) | 61 (37.9) | 136 (36.3) | 0.5888 |

OS, overall survival; PFS, progression-free survival; CR, complete remission; CRi, complete remission with incomplete hematological recovery; ICU, intensive care unit.



DOI: 10.1002/hon

their molecular mutational marker profiles. *NPM1* and *CEBPA* mutations as well as *FLT3-ITD* were equally distributed between the low and high fibrinogen groups.

In a univariate analysis, age <60 years, WBC <10 000/uL, LDH <800 U/L, CRP <5 mg/L, favorable risk classification [11], and plasma fibrinogen level <4.10 g/L were associated with both better PFS and OS (Tables 3a and 3b). Because of the uneven distribution of AML-M0/M1 in both groups, we also included these FAB subtypes in our univariate analysis to adjust for this heterogeneity in the baseline characteristics; however, no effect on survival could be identified. The ISTH DIC score at diagnosis could be assessed in 147 patients, and we found it to be higher in the low fibrinogen group, but it did not affect outcome.

Owing to inevitable heterogeneities in the baseline characteristics and in order to identify an independent effect of fibrinogen levels on clinical outcome, we performed a multivariate Cox regression analysis (Table 4). When adjusting for age, gender, leukocyte count at diagnosis, LDH, adverse risk, *t*(15;17) and *t*(8;21) risk groups, fibrinogen remained a significant predictor (adj. $p = 0.003$), whereas leukocyte count and *t*(15;17) lost their significance (adj. $p = 0.077$ and $p = 0.419$, respectively).

## Discussion

To the best of our knowledge, this is the first study evaluating the prognostic impact of plasma fibrinogen on survival in a large cohort of patients with newly diagnosed AML undergoing intensive chemotherapy induction treatment. Our results suggest that elevated plasma fibrinogen levels determined at diagnosis before initiation of treatment are associated with inferior PFS and OS but not with increased mortality or ICU admission rates during induction therapy in patients with AML. Also, we observed no association between high plasma fibrinogen levels and remission rates in our study population. Therefore, fibrinogen may be useful as a prognostic marker for survival but not as a predictive marker for response to treatment in AML patients undergoing intensive therapy.

Previous reports in cancer patients indicated that plasma fibrinogen levels are of prognostic significance in several solid malignancies including endometrial and ovarian [6,18], renal cell [7], esophageal [19,20], and hepatocellular [21] and non-small cell lung cancer [8,22]. These findings in solid tumors and the fact that determination of fibrinogen is part of the standard diagnostic work-up in AML patients led us to explore the impact of elevated

**Table 3a**. Univariate analysis for progression-free survival

| Progression-free survival *n* (%) | | HR (95% CI) | *P* |
|---|---|---|---|
| Age | | | |
| <60 years | 252 (67.2) | 1.00 | |
| ≥60 years | 123 (32.8) | 1.836 (1.516–2.648) | <0.0001 |
| Gender | | | |
| Female | 165 (44.0) | 1.00 | |
| Male | 210 (56.0) | 1.176 (0.918–1.504) | 0.2012 |
| WBC | | | |
| <10 g/L | 187 (49.9) | 1.00 | |
| ≥10 g/L | 188 (50.1) | 1.749 (1.382–2.271) | <0.0001 |
| LDH | | | |
| <800 U/L | 209 (55.7) | 1.00 | |
| ≥800 U/L | 166 (44.3) | 1.362 (1.070–1.769) | 0.0132 |
| Fibrinogen | | | |
| <4.10 g/L | 214 (57.1) | 1.00 | |
| ≥4.10 g/L | 161 (42.9) | 1.394 (1.097–1.812) | 0.0076 |
| CRP | | | |
| <5 mg/L | 81 (22.9) | 1.00 | |
| ≥5 mg/L | 272 (77.1) | 1.662 (1.179–2.087) | 0.0021 |
| FAB group | | | |
| M0/M1 | 114 (30.4) | 1.00 | |
| Other FAB types | 261 (69.6) | 0.813 (0.613–1.056) | 0.1183 |
| Risk classification | | | |
| Intermediate | 209 (58.1) | 1.00 | |
| Favorable + *t*(15;17) | 93 (37.6) | 0.316 (0.289–0.517) | <0.0001 |
| Favorable | 62 (15.3) | 0.341 (0.318–0.599) | <0.0001 |
| *t*(15;17) | 31 (7.8) | 0.258 (0.281–0.617) | <0.0001 |
| Adverse | 73 (18.8) | 1.499 (1.146–2.197) | 0.0059 |
| ISTH DIC score (*n* = 147) | | | |
| ≤4 | 110/147 (74.8) | 1.00 | |
| >4 | 37 (25.1) | 0.868 (0.554–1.373) | 0.5544 |



DOI: 10.1002/hon

**Table 3b**. Univariate analysis for overall survival

| Overall survival *n* (%) | | HR (95% CI) | *P* |
|---|---|---|---|
| Age | | | |
| <60 years | 252 (67.2) | 1.00 | |
| ≥60 years | 123 (32.8) | 2.035 (1.706–3.091) | <0.0001 |
| Gender | | | |
| Female | 165 (44.0) | 1.00 | |
| Male | 210 (56.0) | 1.202 (0.925–1.558) | 0.1952 |
| WBC | | | |
| <10 g/L | 187 (49.9) | 1.00 | |
| ≥10 g/L | 188 (50.1) | 1.648 (1.277–2.151) | 0.0002 |
| LDH | | | |
| <800 U/L | 209 (55.7) | 1.00 | |
| ≥800 U/L | 166 (44.3) | 1.383 (1.070–1.820) | 0.0139 |
| Fibrinogen | | | |
| <4.10 g/L | 214 (57.1) | 1.00 | |
| ≥4.10 g/L | 161 (42.9) | 1.545 (1.206–2.055) | 0.0009 |
| CRP | | | |
| <5 mg/L | 81 (22.9) | 1.00 | |
| ≥5 mg/L | 272 (77.1) | 1.944 (1.314–2.368) | 0.0002 |
| FAB Group | | | |
| M0/M1 | 114 (30.4) | 1.00 | |
| Other FAB types | 261 (69.6) | 0.797 (0.590–1.051) | 0.1060 |
| Risk classification | | | |
| Intermediate | 209 (58.1) | 1.00 | |
| Favorable + *t*(15;17) | 93 (37.6) | 0.326 (0.295–0.551) | <0.0001 |
| Favorable | 62 (15.3) | 0.327 (0.307–0.612) | <0.0001 |
| *t*(15;17) | 31 (7.8) | 0.313 (0.296–0.695) | 0.0003 |
| Adverse | 73 (18.8) | 1.586 (1.210–2.393) | 0.0024 |
| ISTH DIC score (*n* = 147) | | | |
| ≤4 | 110 (74.8) | 1.00 | |
| >4 | 37 (25.1) | 0.937 (0.576–1.527) | 0.7970 |

WBC, white blood cell; ISTH DIC, International Society for Thrombosis and Haemostasis disseminated intravasal coagulation; HR, hazard ratio; FAB, French–American–British; CRP, C-reactive protein.

**Table 4**. Multivariate analysis for overall survival, simultaneously adjusting for all considered risk factors

| Risk factor | C index | crude HR | crude *p* | adj. HR | adj. *p* |
|---|---|---|---|---|---|
| Age | 0.60 (0.56–0.64) | 1.30 (1.17–1.44) | <0.001 | 1.35 (1.21–1.51) | <0.001 |
| Fibrinogen | 0.57 (0.53–0.61) | 1.16 (1.08–1.25) | <0.001 | 1.14 (1.05–1.25) | 0.003 |
| CRP[1] | 0.62 (0.58–0.66) | 1.26 (1.15–1.37) | <0.001 | — | — |
| Lc | 0.57 (0.53–0.61) | 1.14 (1.05–1.24) | 0.002 | 1.11 (0.99–1.24) | 0.077 |
| LDH | 0.56 (0.52–0.60) | 1.34 (1.12–1.60) | 0.001 | 1.29 (1.02–1.63) | 0.032 |
| Adverse risk | 0.56 (0.53–0.58) | 2.08 (1.54–2.81) | <0.001 | 2.29 (1.66–3.16) | <0.001 |
| Gender (male) | 0.52 (0.49–0.56) | 1.20 (0.92–1.57) | 0.170 | 1.09 (0.83–1.42) | 0.546 |
| *t*(8;21) | — | 0.46 (0.22–0.99) | 0.046 | 0.43 (0.20–0.93) | 0.032 |
| *t*(15;17) | — | 0.33 (0.17–0.64) | 0.001 | 0.74 (0.36–1.54) | 0.419 |
| Tx before 2000 | 0.52 (0.50–0.55) | 0.69 (0.48–0.98) | 0.040 | 1.08 (0.74–1.58) | 0.675 |

CR, C-reactive protein; HR, hazard ratios.
The C index was calculated from the univariate Cox model.
[1]Owing to missing data in a substantial portion of patients, CRP could not be adjusted for in these calculations.

fibrinogen plasma level on survival in AML patients. In particular, we investigated whether results obtained in solid tumors could similarly be seen in AML patients; this is of particular interest because experience in daily practice suggests that very low fibrinogen levels in AML patients are associated with an increased risk of bleeding events. However, we found no evidence of shortened survival rates or increased early death rates in patients with low fibrinogen levels at diagnosis. These findings are in contrast to two prior studies that reported that low fibrinogen at diagnosis



DOI: 10.1002/hon

correlates with increased ICU admissions and early death [23,24]. This difference might be due to our rather aggressive strategy of preventive fibrinogen substitution in case of deregulated hemostasis. We therefore assume that the timely use of blood products and fibrinogen substitution in AML patients with overt DIC is sufficient to control deregulated hemostasis and ultimately prevent early death.

Our analysis suggests an adverse clinical outcome in AML patients with hyperfibrinogenemia at diagnosis of AML, but the detailed mechanisms involved remain to be clarified. The relationship between solid tumors and impaired hemostasis leading to both increased thromboembolic events and bleeding propensity is fairly established [25–31]. However, we observed neither more bleeding events in the low fibrinogen AML group nor more thromboembolic events in the high fibrinogen group in our large cohort of AML patients (data not shown). In the absence of an unbalanced incidence of fatal thrombosis and bleeding events, our data suggest an independent prognostic significance of deregulated hemostasis in AML patients at diagnosis. We intended to further evaluate possible disparities in activation of hemostasis between the low and high fibrinogen group using the ISTH DIC score, which is calculated on the basis of platelets, prothrombin time, D-dimers, and fibrinogen levels. We observed a higher ISTH DIC score in the low fibrinogen group compared with the high fibrinogen group. However, we found no correlation between the ISTH DIC score and survival rates.

Unexpectedly, patients harboring *t*(8;21) had higher fibrinogen levels at diagnosis compared with those without this translocation. Accordingly, the multivariate analysis indicated that both fibrinogen and *t*(8;21) are independent prognostic factors, suggesting an inverse correlation between fibrinogen and *t*(8;21).

A common hypothesis in solid tumors indicates that hyperfibrinogenemia is associated with worse PFS and OS because tumor cells affect hemostasis by activating the coagulation cascade resulting in enhanced thrombin generation. This in turn leads to increased conversion of fibrinogen to fibrin, and the resulting fibrinogen and fibrin fragments stimulate neoangiogenesis thereby facilitating tumor spread [32]. Furthermore, fibrinogen in cooperation with platelets can build a meshwork that entraps tumor cells, enabling them to evade host immunosurveillance [33,34]. However, it remains to be investigated whether such concepts are applicable to AML patients.

As an acute phase protein, fibrinogen is characteristically increased during inflammatory processes. Tumor cells commonly release chemokines, cytokines, and prostaglandins that further promote not only the recruitment of inflammatory cells but also neoangiogenesis, tumor cell proliferation, and metastasis [18,35]. Because fibrinogen acts as an acute phase protein, high fibrinogen levels may be associated with increased early mortality or more frequent ICU admissions during induction treatment as a result of systemic inflammatory response accompanying overt AML at diagnosis. However, our results indicate that elevated fibrinogen levels are not associated with adverse outcome during early treatment—such as day 30 mortality—but with unfavorable PFS and OS rates.

Our data suggest that leukemia-triggered inflammatory response, reflected by increased fibrinogen levels, is associated with inferior outcome. One might speculate that the use of anti-inflammatory drugs, including corticosteroids, during the induction chemotherapy might affect outcome. As an institutional policy, all patients in this study received steroids as antiemetic treatment limited to the initial days of induction chemotherapy. The impact of such steroid treatment on clinical outcome depending on varying fibrinogen levels at diagnosis is unknown and can only be clarified in an adequately powered prospective trial. Strengths of our study are the inclusion of a large number of consecutive patients, and that we could demonstrate the prognostic significance of fibrinogen on survival in both univariate and multivariate analyses. Furthermore, we were able to confirm this association with different cut-offs by using quartile patient groups of fibrinogen plasma levels. Obvious limitations of our study are its retrospective single-center design and the lacking validation in an independent AML cohort. Consequently, the results of this study suggest that there is a rationale for adequately powered prospective studies to confirm the prognostic significance of fibrinogen levels as a biomarker for survival in AML patients.

## Conclusion

In summary, our data identify a prognostic role of fibrinogen levels at diagnosis on survival in a large cohort of AML patients undergoing intensive treatment. Because fibrinogen is routinely assessed in patients with acute leukemia at diagnosis, it can easily be incorporated in future risk assessment algorithms.

### Acknowledgement

This work was supported by grants from the Bernische Krebsstiftung (to TP), the Bernese Cancer League (to TP) and from the EMPIRIS Stiftung (to TP).

### Conflict of interest

The authors declare no conflict of interests.

## References

1. Hoppe B. Fibrinogen and factor XIII at the intersection of coagulation, fibrinolysis and inflammation. *Thromb Haemost* 2014; **112**: 649–658.

2. Collen D, Tytgat GN, Claeys H. Metabolism and distribution of fibrinogen. I. Fibrinogen turnover in physiological conditions in humans. *Br J Haematol* 1972; **22**: 681–700.
3. Tennent GA, Brennan SO, Stangou AJ. Human plasma fibrinogen is synthesized in the liver. *Blood* 2007; **109**: 1971–1974.
4. Danesh J, Lewington S, Thompson SG. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA* 2005; **294**: 1799–1809.
5. Palumbo JS. Mechanisms linking tumor cell-associated procoagulant function to tumor dissemination. *Semin Thromb Hemost* 2008; **34**: 154–160.
6. Seebacher V, Polterauer S, Grimm C. The prognostic value of plasma fibrinogen levels in patients with endometrial cancer: a multi-centre trial. *Br J Cancer* 2010; **102**: 952–956.
7. Pichler M, Hutterer GC, Stojakovic T. High plasma fibrinogen level represents an independent negative prognostic factor regarding cancer-specific, metastasis-free, as well as overall survival in a European cohort of non-metastatic renal cell carcinoma patients. *Br J Cancer* 2013; **109**: 1123–1129.
8. Sheng L, Luo M, Sun X. Serum fibrinogen is an independent prognostic factor in operable nonsmall cell lung cancer. *Int J Cancer* 2013; **133**: 2720–2725.
9. Weltermann A, Pabinger I, Geissler K. Hypofibrinogenemia in non-M3 acute myeloid leukemia. Incidence, clinical and laboratory characteristics and prognosis. *Leukemia* 1998; **12**: 1182–1186.
10. Chang H, Kuo MC, Shih LY. Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia. *Eur J Haematol* 2012; **88**: 321–328.
11. Döhner H, Estey EH, Amadori S. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010; **115**: 453–474.
12. Taylor FB Jr, Toh CH, Hoots WK. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001; **86**: 1327–1330.
13. Bennett JM, Catovsky D, Daniel MT. Proposals for the classification of the acute leukaemias. French–American–British (FAB) co-operative group. *Br J Haematol* 1976; **33**: 451–458.
14. Harris NL, Jaffe ES, Diebold J. The World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting – Airlie House, Virginia, November, 1997. *Hematol J* 2000; **1**: 53–66.
15. Jaffe ES, Harris NL, Stein H. Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues (3rd edn). WHO Classification of Tumours, IARC Press: Lyon, France 2001.
16. Swerdlow SH, Campo E, Harris NL. 4th ed. WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues; IARC Press: Lyon, France 2008.
17. Cheson BD, Bennett JM, Kopecky KJ. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol* 2003; **21**: 4642–4649.
18. Polterauer S, Grimm C, Seebacher V. Plasma fibrinogen levels and prognosis in patients with ovarian cancer: a multicenter study. *Oncologist* 2009; **14**: 979–985.
19. Takeuchi H, Ikeuchi S, Kitagawa Y. Pretreatment plasma fibrinogen level correlates with tumor progression and metastasis in patients with squamous cell carcinoma of the esophagus. *J Gastroenterol Hepatol* 2007; **22**: 2222–2227.
20. Matsuda S, Takeuchi H, Fukuda K. Clinical significance of plasma fibrinogen level as a predictive marker for postoperative recurrence of esophageal squamous cell carcinoma in patients receiving neoadjuvant treatment. *Dis Esophagus* 2014; **27**: 654–661.
21. Kinoshita A, Onoda H, Imai N. Elevated plasma fibrinogen levels are associated with a poor prognosis in patients with hepatocellular carcinoma. *Oncology* 2013; **85**: 269–277.
22. Kim KH, Park TY, Lee JY. Prognostic significance of initial platelet counts and fibrinogen level in advanced non-small cell lung cancer. *J Korean Med Sci* 2014; **29**: 507–511.
23. Schellongowski P, Staudinger T, Kundi M. Prognostic factors for intensive care unit admission, intensive care outcome, and post-intensive care survival in patients with *de novo* acute myeloid leukemia: a single center experience. *Haematologica* 2011; **96**: 231–237.
24. Krug U, Röllig C, Koschmieder A. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet* 2010; **376**: 2000–2008.
25. Sun NC, McAfee WM, Hum GJ. Hemostatic abnormalities in malignancy, a prospective study of one hundred eight patients. Part I. Coagulation studies. *Am J Clin Pathol* 1979; **71**: 10–16.
26. Costantini V, Zacharski LR, Moritz TE. The platelet count in carcinoma of the lung and colon. *Thromb Haemost* 1990; **64**: 501–505.
27. Luzzatto G, Schafer AI. The prethrombotic state in cancer. *Semin Oncol* 1990; **17**: 147–159.
28. Symbas NP, Townsend MF, El-Galley R. Poor prognosis associated with thrombocytosis in patients with renal cell carcinoma. *BJU Int* 2000; **86**: 203–207.
29. Ikeda M, Furukawa H, Imamura H. Poor prognosis associated with thrombocytosis in patients with gastric cancer. *Ann Surg Oncol* 2002; **9**: 287–291.
30. Levi M. Disseminated intravascular coagulation in cancer patients. *Best Pract Res Clin Haematol* 2009; **22**: 129–136.
31. Ay C, Dunkler D, Pirker R. High D-dimer levels are associated with poor prognosis in cancer patients. *Haematologica* 2012; **97**: 1158–1164.
32. Wang X, Wang E, Kavanagh JJ. Ovarian cancer, the coagulation pathway, and inflammation. *J Transl Med* 2005; **3**: 25.
33. Biggerstaff JP, Seth N, Amirkhosravi A. Soluble fibrin augments platelet/tumor cell adherence *in vitro* and *in vivo*, and enhances experimental metastasis. *Clin Exp Metastasis* 1999; **17**: 723–730.
34. Palumbo JS, Talmage KE, Massari JV. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. *Blood* 2005; **105**: 178–185.
35. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860–867.


## Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.





DOI: 10.1002/hon