Can biomarkers of coagulation, platelet activation, and inflammation predict mortality in patients with hematological malignancies?

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ABSTRACT

Background: Patients with cancer commonly demonstrate laboratory evidence for hypercoagulability. Coagulation and inflammation play a role in the pathophysiology of hematological malignancies and the correlation between hypercoagulability and inflammation with tumor outcomes and the patient’s prognosis are well studied.

Objective: To identify an association between hemostasis activation, fibrinolysis and inflammation with mortality in patients with hematological malignancies to determine their prognostic significance.

Methods: This study is a prospective observational cohort study; Hypercoagulability and inflammatory biomarkers including: (1) Coagulation and fibrinolysis activation Markers (D-dimer, Fibrinogen, Antithrombin, plasminogen activator inhibitor 1 [PAI-1]); (2) Endothelium and platelet activation Markers (von Willebrand Factor [vWF], soluble P-selectin); and (3) Inflammation Markers (Tumor necrosis factor alpha [TNF-α], Interleukin-6 [IL-6]) were assayed on a group of 171 patients with hematological malignancies at time of diagnosis. They have been followed up for an average period of 416.8 days with an endpoint of mortality.

Results: Sixty patients died during follow up. There were statistically significant associations between Plasma cell dyscrasias mortality and ECOG performance status (P value:<0.005), Hemoglobin level (P value: 0.04), serum Albumin level (P value: 0.001), vWF (P value: 0.006) and IL-6 (P value 0.015), and between lymphoproliferative disorders mortality and presence of B symptoms (P value: 0.02), ECOG performance status (P value:<0.02), serum Albumin level (P value: 0.038), Antithrombin (P value: 0.004).

Conclusion: Some biomarkers of coagulation and inflammation showed statistically significant associations with plasma cell dyscrasias mortality (vWF and IL-6) and lymphoproliferative disorders mortality (Antithrombin) and potentially could be used as prognostic markers.

KEYWORDS
Mortality; hematologic neoplasms; biomarkers; coagulation; inflammation

Introduction

The relationship between cancer and venous thromboembolism (VTE) has been recognized for many years and Armand Trousseau was the first to describe a clinical association between thrombosis and undiagnosed cancer over 100 years ago [1].

Patients with cancer commonly demonstrate laboratory evidence for subclinical hypercoagulability even in the absence of overt clinical thrombosis. Consideration of the pathophysiology of this hypercoagulability is important to the design of appropriate intervention measures either to prevent or treat thrombohemorrhagic complications of the hematologic malignancies [2].

The pathogenesis of hypercoagulability in cancer is complex and multifactorial. Multiple hemostatic derangements are proved to exist with malignancies, as high levels of plasma by-products of clotting reactions (i.e. prothrombin fragment 1+2 [F1+2], D-dimer, fibrinopeptide A, and thrombin–antithrombin complex), or high levels of circulating microparticles produced by tumor cells and platelets as well as an acquired protein C resistance [3]. On the other hand, hemostatic proteins and reactions play a role in the process of angiogenesis, tumor cell invasion, tumor progression, and metastatic spread [4].

In the last decade, many studies looked at the role of hypercoagulability and inflammation in the pathophysiology of hematological malignancies and the extent of their correlation with tumor stage, outcomes, and the patient’s prognosis [5–9].

This study was a prospective observational cohort study aiming to identify an association between the activation of hemostasis and fibrinolysis as well as inflammation with mortality in patients with hematological malignancies to determine their role in prognosis.

Patients and methods

The study was conducted on a group of 171 patients with malignant hematological conditions treated in...
the hematology unit in Cairo University hospital between 2013 and 2015. Adult patients with newly diagnosed hematologic malignancies or relapse of disease after complete or partial remission were considered for inclusion in the study. Exclusion criteria were overt bacterial or viral infection within the previous 2 weeks, venous or arterial thromboembolism within the previous 3 months, and anticoagulation with vitamin K antagonists or low molecular weight heparin (LMWH). Patients were allowed to take antiplatelet agents and treated with LMWH as thromboprophylaxis during their hospital stay or myeloma patients on immunomodulatory drugs (IMiDs), following surgery or radiotherapy within the previous 2 weeks and chemotherapy within the previous 3 months to exclude a transient influence of these interventions on the hemostatic system.

Laboratory and/or histological testing confirmation of the diagnosis of hematological malignancy were a prerequisite. Hypercoagulability was assessed at entry into the study by measuring the circulating levels of the following parameters: (1) Markers of coagulation and fibrinolysis activation [D-dimer, fibrinogen, antithrombin, plasminogen activator inhibitor 1 (PAI-1)]; (2) Markers of endothelium and platelet activation [von Willebrand Factor (vWF), soluble P-selectin]; and (3) Markers of inflammation [Tumor necrosis factor alpha (TNF-α), Interleukin-6 (IL-6)]. End point was mortality.

Ten milliliters of blood (drawn directly by venipuncture) were collected from each subject and divided into two sterile citrate vacutainers (for fibrinogen, AT III, P-selectin, vWF, PAI-1 antigen, and D-Dimer) and one sterile Ethylenediaminetetraacetic acid (EDTA) vacutainer (for IL-6 and TNF-α).

Samples were centrifuged immediately at 4000 RPM for 15 minutes and plasma was separated into aliquots and stored at −20°C then brought to room temperature prior to the assay. Hemolysed or clotted samples were discarded.

Commercial ELISA methods were used to measure plasma levels of D-dimer (Technozyn®, Technoclone, Vienna, Austria), PAI-1, vWF antigen, TNF-α, and IL-6 (all from AssayMax®, AssayPro, St. Charles, MO, U.S.A.), human fibrinogen (GenWay, San Diego, CA, U.S.A.), human pselectin (RayBio, Norcross, GA, U.S.A.). The ELISA biomarkers were performed according to the manufacturer’s instructions. Antithrombin analysis was performed by Radial Immunodiffusion in the range of 15–20 mg/dl (Haemtech, Essex Junction, VT, U.S.A.). PT was performed using neoplastone reagent (Stago Coagulation AQ6analyzer, Stago, Parsippany, NJ, U.S.A.). All analyses were performed within 5 months from blood collection in a blinded fashion in the central laboratory of Kasr Alainy Faculty of Medicine, Cairo University, Egypt.

Statistical methods used were as follows: Statistical package for social science program version 16.0 was used for the analysis of data. Data were summarized as mean, standard deviation (SD). Independent samples’ t-test was used for parametric quantitative variables; Mann–Whitney test was used for the analysis of non-parametric quantitative data. Chi square was used for the analysis of qualitative data. Receiver operating characteristic (ROC) curve was used for determining cut-off values for laboratory biomarkers. Kaplan–Meier method and Cox proportional hazard model were used for survival analysis. p-value was considered significant if <0.05.

Results

Patient demographics

The study included 171 patients with malignant hematological conditions followed up for an average period of 416.82 days with an endpoint of mortality. The mean age was 48.6 years with 79 (46.2%) female patients and 92 (53.8%) male patients. Out of 171 patients, 48 (28.1%) were diagnosed to have lymphoproliferative disorders (7 had Hodgkin lymphoma, 14 had follicular lymphoma, 9 had diffuse large B cell lymphoma, 12 had chronic lymphocytic leukemia, 3 had hairy cell leukemia, 2 had T-cell lymphoma, and 1 had Burkitt lymphoma, 40 (23.4%) myeloproliferative neoplasms (26 had chronic myeloid leukemia, 6 had polyclinical and lymph nodes missed 3, had essential thrombocythemia, and 5 had primary myelofibrosis), 38 (22.2%) were diagnosed to have acute myeloid leukemia (AML) (35) (or myelodysplastic syndrome progressed to AML(3)), 19 (11.1%) were diagnosed to have acute lymphoblastic leukemia (ALL) (all are B-ALL), 26 (15.2%) were diagnosed to have plasma cell dyscrasias (21 had myeloma, 2 had AL amyloidosis, 3 had Waldenström’s macroglobulinemia). All patients were newly diagnosed except six had relapsed disease (two with AML, two with ALL, and two with Follicular lymphoma).

One hundred and ten (64.3%) patients had one or more of constitutional manifestations (fever, weight loss, excessive sweating), 77 (45%) patients had one or more co-morbidities including diabetes mellitus, hypertension, ischemic heart disease, renal impairment, liver cell failure, tuberculosis, psoriasis, Parkinsonism, Guillain–Barre, and hypothyroidism. Eastern Cooperative Oncology Group (ECOG) performance status showed a mean of 2.11, SD of 1.087, Body mass index (BMI) showed a mean of 26.14 kg/m², and SD of 5.14. 115 (67.3%) patients had organomegaly (hepatomegaly and/or splenomegaly), 51 patients (29.8%) had lymphadenopathy. Thirteen (7.5%) patients underwent a surgical procedure (all were lymph node biopsies), 28 (16.4%) had a central venous access device CVAD inserted, 156 (91.2%) patients received chemotherapy, two (1.2%) patients received radiotherapy, two patients received IMiDs
Mortality and laboratory biomarkers

Sixty (35.1%) patients died during follow-up. Forty-five (75%) patients died within 6 months after diagnosis, 11 (18.3%) patients died within 12 months, and 4 (6.7%) died within 18 months.

Out of 60 patients who died during follow-up, 34 (56.7%) died of disease progression, 17 (28.3%) died of infection, 3 (5%) died of pulmonary embolism (diagnosed by CT pulmonary angiography), 3 (5%) died of hepatic failure, 2 (3.3%) died of heart failure, and 1 (1.7%) died of intracranial bleeding (diagnosed by CT head).

There were statistically significant associations between plasma cell dyscrasias mortality and ECOG performance status (p value: <0.005), hemoglobin level (p value: 0.04), serum albumin level (p value: 0.001), vWF (p value: 0.006), and IL-6 (p value 0.015) (Table 1).

For prediction of plasma cell dyscrasias mortality, ROC curve of hemoglobin showed that a level of 6.8 g/dl showed the highest likelihood ratio (LR) of 3.78 with a sensitivity of 66.7% and a specificity of 87%. ROC curve of albumin level showed that a level of 2.4 g/dl showed the highest LR of 14.3 with a sensitivity of 88.9% and a specificity of 99%. ROC curve of vWF showed that a level of 3.31 mU/ml showed the highest LR of 6.95 with a sensitivity of 77.8% and a specificity of 88.2%. ROC curve of IL-6 levels showed that a level of 5.15 pg/ml showed the highest LR of 2.2 with a sensitivity of 77.8% and a specificity of 65% (Figure 1).

There were statistically significant associations between mortality of patients with lymphoproliferative disorders and the presence of B symptoms (p value: 0.04), serum albumin level (p value: 0.001), vWF (p value: 0.006), and IL-6 (p value 0.015), and between mortality of patients with lymphoproliferative disorders and the presence of B symptoms (p value: 0.02), ECOG performance status (p value: <0.02), serum albumin level (p value: 0.038), antithrombin (p value: 0.004).

In hematological diseases, TNF-α has been shown to be a regulator of the growth of hematopoietic stem and progenitor cells [8]. In HL, elevated levels strongly predicted shorter free-from-progression survival and overall survival of the patients [10]. TNF-α and its receptors were also elevated in patients with NHL and could represent valuable prognostic markers in those individuals [11,12]. Studies also showed that TNF-α may cooperate with other cytokines, such as IL-6, IL-10, and IL-2 in vivo to increase NHL cell proliferation [13]. In myeloma, TNF-α plays an important role in the proliferation and survival of plasma cells [14] as reduced apoptosis rate is mediated partly by TNF-α [15,16]. A study has found that mean level of TNF-α was significantly higher in AML patients than in the controls [17]. High serum TNF-α level is an adverse prognostic factor for overall and event-free survival in AML patients [7]. However, in our study plasma TNF-α level did not show any statistically significant associations with mortality of any of patient groups.

IL-6 plays a vital role in solid and hematological tumors, as elevated serum levels of IL-6 are often correlated with adverse prognosis, and probably contribute to constitutional manifestations as weight loss, night sweats, fever, and other paraneoplastic symptoms [18,19]. IL-6’s role as a growth and survival factor in multiple myeloma is well established [20]. IL-6 is also a potent osteoclast-activating factor, and contributes to the development of bone lesions. Elevated levels of IL-6 and soluble IL-6 receptors frequently present in the BM, plasma, and serum of myeloma patients are considered as a poor prognostic indicator [9]. High levels of IL-6 are also present in Castleman’s disease, and are associated with severe inflammatory symptoms, increased levels of acute-phase proteins, and hypergammaglobulinemia [21]. In many cases, serum IL-6 or sIL-6R levels are elevated for low- and high-grade non-Hodgkin’s lymphomas, Hodgkin’s disease, and in adult T-cell leukemia/lymphoma [9]. Our study emphasized the aforementioned findings with myeloma and higher level of serum IL-6 was significantly associated with increased mortality in patients with plasma cell dyscrasias; further studies are needed to clarify the potential use of IL-6 as a prognostic marker and its inclusion in myeloma scoring.

Discussion

Our study showed statistically significant associations between plasma cell dyscrasias mortality and ECOG performance status (p value: <0.005), hemoglobin level (p value: 0.04), serum albumin level (p value: 0.001), vWF (p value: 0.006), and IL-6 (p value 0.015), and between mortality of patients with lymphoproliferative disorders and the presence of B symptoms (p value: 0.02), ECOG performance status (p value: <0.02), serum albumin level (p value: 0.038), antithrombin (p value: 0.004).

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|                                | **Lymphoproliferative disorders** | **Myeloproliferative disorders** | **Acute myeloid leukemia** | **ALL** | **Plasma cell dyscrasias** |
|--------------------------------|-----------------------------------|----------------------------------|---------------------------|---------|--------------------------|
|                                | All patients (n=48)               | Survived (n=30)                  | Patients died (n=18)      | p value |                          |
| **Age range**                  | 52.4 (14.6)                       | 18–76                            | 50.2 (16.8)               | 56 (9.2) | 0.18                     |
| **Presence of comorbidities N (%)** | 36 (75)                           | 19 (63.3)                        | 17 (94.4)                 | 0.02*   |
| **ECOG performance mean (± SD)** | 2.1 (1.1)                         | 1.8 (0.99)                       | 2.7 (1)                   | 0.02*   |
| **BMI mean (± SD)**            | 26.2 (5.3)                        | 25.9 (5.1)                       | 26.6 (5.8)                | 0.65    |
| **Hemoglobin level (g/dl) mean (± SD)** | 11.9 (1)                         | 11.8 (1.09)                      | 12.3 (0.98)               | 0.01*   |
| **Prothrombin time (seconds) mean (± SD)** | 29.2 (21.5)                     | 26.8 (6.5)                       | 28 (2)                   | 0.67    |
|                                | 3.3 (0.8)                         | 3.5 (0.77)                       | 2.9 (0.9)                 | 0.038*  |
| **LDH (U/L) mean (± SD)**      | 603 (613)                         | 497.2 (558)                      | 761.5 (671.9)             | 0.13    |
| **ESR (mm/hour) mean (± SD)**  | 75.4 (45)                         | 69.2 (45.6)                      | 80 (46.4)                 | 0.23    |
| **D-Dimer (ng/ml) mean (± SD)**| 823.8 (819)                       | 590.3 (529)                      | 423.9 (592)               | 0.21    |
| **Fibrinogen (mg/ml) mean (± SD)** | 864.3 (8743)                   | 1002 (2417)                      | 650 (1093)                | 0.65    |
| **Antithrombin (mg/dl) mean (± SD)** | 20.6 (9.3)                       | 23.6 (9.4)                       | 15.8 (8.2)                | 0.004*  |
| **PAI-1 (ng/ml) mean (± SD)**  | 29.2 (21.5)                       | 28.6 (20.3)                      | 30.3 (24)                 | 0.79    |
| **P-selectin (ng/ml) mean (± SD)** | 26.6 (26.2)                     | 23.7 (24.7)                      | 31.2 (28.4)               | 0.11    |
| **TFN-a (ng/ml) mean (± SD)**  | 3.3 (2.6)                         | 3.5 (2.9)                        | 3.3 (2.6)                 | 0.27    |
| **IL-6 (pg/ml) mean (± SD)**   | 12.5 (27.7)                       | 12.6 (33.8)                      | 12.4 (13.2)               | 0.45    |
| **Note:** Indicator (*) and shades in Table 1 are added for statistically significant findings.
system, and to elaborate the use of IL6 antagonists in myeloma therapeutic strategies.

Elevated D-dimer levels are not specific and may also be observed in many clinical settings, such as cancer, pregnancy, and infectious diseases or following trauma and surgery [5]. In Ay’s study published in 2012, high D-dimer levels were associated with poor overall survival and increased mortality risk in cancer patients including patients with hematological malignancies (p value was 0.001 in lymphoma and 0.65 in myeloma) [5]. Yet, in our study, D-dimer did not show any statistical significance with any of the hematological malignancies concerning mortality.

Fibrinogen exerts well-known roles in hemostasis as a substrate for fibrin clot formation and by binding to platelets to trigger platelet aggregation. Additionally, fibrinogen acts as an acute-phase protein and is elevated during inflammatory processes [22]. In 2016, Berger et al. showed that overall survival in AML was significantly better in the low fibrinogen level (27.3 vs 13.5 months; \( p = 0.0009 \)) as well as progression-free survival (12.3 vs 7.8 months; \( p = 0.0076 \)) [23]. However, in our study, fibrinogen levels did not show any prognostic impact on hematological malignancies.

Antithrombin is a hepatocyte-produced protein with both intravascular and extravascular coagulation properties, and it is present normally in blood and lymph both in soluble form and bonded to thrombin-forming reversible antithrombin–thrombin complexes [24]. Some studies showed lower concentrations of antithrombin in advanced disease with poorer prognosis [25–27]. In studies including patients with lymphoma, lowered levels of serum antithrombin have been characteristically discovered in active disease.

Whereas successful treatment appears to normalize values, but there are still statistically significant differences between groups of lymphoma patients versus controls [28]. Our study supports these findings and lower antithrombin is associated with poorer prognosis in lymphoproliferative malignancies (p value: 0.004*). This can be explained by reduced hepatic synthesis of antithrombin in lymphoma patients, as it was also found in our study that lower serum albumin levels have a negative impact on our patients with lymphoproliferative disorders, in addition to the fact that elevated thrombin production in cancer patients would bind with soluble thrombin, causing its increased consumption. This finding could encourage further studies to elaborate the potential use of antithrombin and albumin as prognostic markers in lymphoproliferative disorders.

PAI-1 is an essential component of the plasminogen–plasmin system and involved in the regulation of many physiologic processes and in the pathogenesis of many disorders including cancer [29,30]. PAI-1 levels can be used as a prognostic marker for thromboembolic complications in patients with cancer, and veno-occlusive disease in the post-bone marrow transplantation setting [29]. Although elevated levels of PAI-1 have been found in leukemic cells, mainly in lysates of myeloid origin [31], but to the best of our knowledge, no studies were conducted to demonstrate the impact of high levels of PAI-1 on the prognosis of hematological malignancies and our study did not demonstrate any relation between serum PAI-1 levels and prognosis of blood cancers.

Higher plasma vWF concentrations are recognized in solid tumors and associated with advanced tumor
stage and poorer prognosis [32–34]. A recently published study showed elevated vWF level in 45 patients with leukemia and lymphoma [6]. In 2003, Minnema et al. showed that Higher FVIII:C/VWF-Ag levels are found in patients with active myeloma [35] and in a previously published study of 72 patients with Waldenström’s macroglobulinemia (WM) surprisingly very high VWF:Ag was found in 59% of patients with an association with shorter survival [36]. Also Kastritis et al. showed, in 2016, that high vWF:Ag levels are associated with poorer prognosis in patients with AL amyloidosis, independently of other features of the disease or cardiac biomarkers [37]. In our study, plasma cell dyscrasias patients had poorer prognosis with higher level of vWF (p value: 0.006) as those patients are likely to have more active disease with more microenvironment interactions between plasma cells and endothelial cells and increased bone marrow angiogenesis. We suggest that VWF:Ag may provide additional prognostic information to the present international scoring systems for myeloma and WM (ISS myeloma, ISSWM) which are built as a combination of age and covariates mainly related to tumor burden and adverse cytogenetics.

Selectins are lectin-like adhesion molecules and are involved in lymphocyte extravasation, especially during inflammation and cancer metastasis. Increased soluble P-selectin concentrations are associated with VTE [38]. Concerning hematological malignancies, Muz at al. showed that inhibiting the interaction between myeloma cells and endothelial and stromal cells via P-selectin inhibitors decreased proliferation in myeloma cells [39]. It was found also that soluble L selectin is expressed and released by AML blast cells and soluble E and soluble L selectins and cellular L selectin may be useful prognostic markers in evaluating AML patients at diagnosis [40]. However, P-selectin level did not show any prognostic impact on our patients.

Serum albumin provides a simple estimator of visceral protein function. Malnutrition and inflammation suppress albumin synthesis [41]. Proinflammatory cytokines and growth factors are released as part of the systemic inflammatory response to the tumor, and lower serum albumin concentration may be due to the production of cytokines, such as IL-6, which modulate the production of albumin by hepatocytes [42]. It is well known that serum albumin is an important prognostic marker in myeloma [43]. In our study, lower serum albumin was significantly associated with poorer prognosis in lymphoproliferative neoplasms and plasma cell dyscrasias and this goes in accordance with myeloma international scoring system; however, albumin is not included in any of the current lymphoproliferative disorders prognostic systems.

Limitations of this study included the relative small number of patients, which caused the non-parametric nature of some variables, practical uneasiness of post-mortem autopsy as a tool for the diagnosis of vascular events as a cause of sudden unexplained death; also hereditary thrombophilia screening was not performed for the patients.

In conclusion, some biomarkers of coagulation and inflammation showed statistically significant associations with hematological malignancies concerning plasma cell dyscrasias mortality, VWF with a cut-off level of >3.31 mU/ml (reflecting increased angiogenesis), and IL-6 with a cut-off level of >5.15 pg/ml (with the possibility of using of IL6 antagonists in therapeutic strategies) may provide additional prognostic information to the present international scoring systems for myeloma and WM (ISS myeloma, ISSWM). With lymphoproliferative disorders mortality, antithrombin with a cut-off level of <16.25 mg/dl (due to reduced hepatic synthesis and increased consumption) potentially could be added to the current prognostic scores.

Disclosure statement
No potential conflict of interest was reported by the authors.

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