Original Article
Clinical factors predictive of mortality in acute leukemia patients with febrile neutropenia

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Abstract: Background: Acute leukemia is mainly treated with chemotherapy leading to febrile neutropenia (FN). There is limited data on clinical factors predictive of mortality in adults with acute leukemia and FN. Methods: This was a retrospective cohort study and enrolled adult patients, diagnosed as acute leukemia, and developed FN. The eligible patients were admitted and followed up with mortality as the primary outcome. A stepwise, multivariate logistic regression analysis was used to find predictors for mortality. Results: There were 203 patients met the study criteria. Of those, 14 patients died (6.89%). AML was the most common type of acute leukemia with FN (64.04%). There were five remaining factors in the final model: AML, FN at admission, prolong broad spectrum antibiotics, lower respiratory tract infection, and Aspergillosis. Only lower respiratory tract infection was significant with adjusted odds ratio of 7.794 (95% CI of 1.549, 39.212). The Hosmer-Lemeshow Chi square was 2.74 (*p* value 0.907). The lower respiratory tract infection group had higher proportions of Gram negative and fungus than the non-lower respiratory tract infection group; specifically *E. coli* (p 0.003), and *Aspergillus* (P < 0.001). Conclusions: There were two independent predictors of mortality in acute leukemia patients with FN: septic shock and lower respiratory tract infection regardless of leukemia type or pathogen. *E. coli* and *Aspergillus* were more common in those with lower respiratory tract infection than those without. No specific pathogens were found in cases of septic shock.

Keywords: Acute myeloid leukemia, *aspergillus*, *escherichia*

Introduction

Acute leukemia is a hematologic malignancy: mainly acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL). There were 14,400 cases diagnosed in the United States in 2012 [1]. The incidence rates of AML and ALL were 2.7 and 1.5 per 100,000 people. The mainstay treatment for acute leukemia is chemotherapy which may lead to febrile neutropenia (FN). The mortality rate in acute leukemia with FN was reported to be the highest mortality rate over other cancers at 23.6% [2].

A previous study found that the mortality rate of FN was 32% in cancer patients presenting to the Emergency Department [3]. The same study also found that there were five independent factors of death in 200 FN patients [3]. These factors included low platelet count, pulmonary infiltration, low serum protein, high respiratory rate, and MASCC score less than 21 (highest adjusted odds ratio of 9.20). However, this study was conducted in cancer patients, not specific to acute leukemia patients and infectious pathogens were not included in the analysis.

In acute leukemia, there are several factors associated with mortality [4-7]. A report from the California Cancer Registry found that older age, co-morbid diseases, bleeding, and organ failure increased the risk of death [8]. Another study from Brazil found that high APCHE II score and hemodialysis were independently associated with mortality with *p* values of 0.038 and 0.006, respectively, but that FN was not [9]. This study aimed find mortality predictors specific to adults with acute leukemia and FN.

Methods

Study population

This was a retrospective cohort study conducted at Srinagarind Hospital, a University Hospital,

Khon Kaen University. This study was a part of the acute leukemia research project. This subgroup study included adult patients, diagnosed as acute leukemia, and developed FN. The diagnosis of FN was made by presence of fever with either absolute neutrophil count of less than 500 cell/mm³ or less than 1,000 cell/mm³ with expected to fall below 500 cell/mm³. The eligible patients were admitted and followed up with mortality as the primary outcome. The study period was between January 1st, 2013 and December 31st, 2015. The study protocol was approved by Khon Kaen University Ethics Committee in Human Research (Thailand; HE591013). Informed consent was not required due to the study being based on retrospective data collection.

Operation definitions and data collection

Data of eligible patients were retrieved from admitted medical charts. The studied variables included baseline characteristics, types of leukemia, acute leukemia treatment regimens, leukemic profiles such as blast in bone marrow, Sites of infection, types of pathogens, other treatments, and treatment outcomes including hospital stays, and mortality. Sites of infection defined by clinical findings and/or evidence from culture such as lower respiratory tract infection (LRI) defined by presence of new pulmonary infiltration with or without positive of sputum culture. Causative pathogens were defined if positive by culture with clinical confirmation. Prolong broad spectrum antibiotics were treatment with broad spectrum antibiotics over 10 days. Other clinical variables were also studied including duration of fever, serum albumin level, total parenteral nutrition, current steroid use, septic shock, and serum galactomannan. Septic shock was defined by the presence of hypotension requiring vasopressors to maintain a mean blood pressure of 65 mmHg after adequate fluid therapy with evidence of infection [10].

Statistical analyses

Data were categorized by mortality outcomes as survived or death. Descriptive statistics were used to compare differences between both groups. Predictors for mortality were calculated by using logistic regression analysis. A univariate logistic regression was used to compute unadjusted odds ratio and a *p* value.

Those factors with a *p* value by univariate logistic analysis of less than 0.25 or potential factors from previous study if available were put in the subsequent multivariate logistic regression analysis. A stepwise method was used to find the strongest predictors. A goodness of fit of the final model was tested by Hosmer-Lemeshow method with a good fit if a *p* value of over 0.05. Results were presented as median (range), number (percentage), *p* values, and unadjusted/adjusted odds ratio with 95% confidence interval (CI). Subgroup analyses for pathogen identification were made according to independent variables. The statistical analyses were performed by STATA software, version 10.1 (College Station, Texas, USA).

Results

Baseline characteristics

There were 203 patients met the study criteria. Of those, 14 patients died (6.89%). AML was the most common type of acute leukemia with FN (64.04%). The median ICU stay was slightly longer in the death group than the survival group (8 vs 7 days; p 0.679) but the median hospital stay was shorter in the death group (25 vs 28 days; p 0.897) as shown in **Table 1**. There were 10 significant factors between these two groups including hypomethylating regimen, FN at admission, GCSF treatment, duration of fever, persistent fever at day 4th, presence of catheter, lower respiratory tract infection, fungal infection, Aspergillus infection, and Candida infection.

Predictors for mortality and pathogens

These 10 factors plus other potential factors (age, sex, serum albumin, types of acute leukemia, blast percentage, neutrophil count, septic shock and prolong broad spectrum antibiotics) were put in the multivariate logistic regression analysis, stepwise method. There were seven remaining factors in the final model: AML, FN at admission, GCSF, prolong broad spectrum antibiotics, septic shock, lower respiratory tract infection, and aspergillosis (**Table 2**). Septic shock and lower respiratory tract infection was significant with adjusted odds ratio of 7.461 (95% CI of 1.101, 50.524) and 7.794 (95% CI of 1.549, 39.212). The Hosmer-Lemeshow Chi square was 4.26 (*p* value 0.833). The identified pathogens were classified by lower respiratory

Table 1. Baseline characteristics and clinical features of acute leukemia patients with febrile neutropenia (FN) categorized by mortality

Factors	Survival n = 189	Death n = 14	p value
Age, years	40 (18-71)	46 (26-65)	0.211
Male	91 (48.15)	6 (42.86)	0.786
Body mass index, kg/m^2	21.64 (13.80-41.14)	23.33 (16.00-39.06)	0.364
Body surface area, m^2	1.59 (1.21-2.47)	1.58 (1.22-2.11)	0.773
Types of leukemia			
AML	121 (64.02)	9 (64.29)	0.999
APL	10 (5.29)	2 (14.29)	0.196
ALL	40 (21.16)	2 (14.29)	0.739
Treatment regimen			
I3A7	142 (75.94)	11 (78.57)	0.999
I2A5	5 (2.67)	1 (7.14)	0.355
ALL induction	40 (21.39)	2 (14.29)	0.739
Hypomethylating	35 (18.72)	6 (42.86)	0.042
% Blast in blood smear	54 (0-98)	7 (0-99)	0.168
% Abnormal Promyelocyte and blast in BM	75 (20-100)	90 (30-99)	0.053
ANC100	167 (88.36)	13 (92.86)	0.999
ANC lowest	5.2 (0-521)	3 (0-184)	0.748
FN at admission	40 (26.32)	7 (77.78)	0.003
Onset of FN	10 (1-39)	8 (5-10)	0.366
Neutropenic time	8 (1-44)	10 (5-47)	0.257
G-CSF	72 (38.10)	1 (7.14)	0.020
Duration of fever	4 (1-57)	17 (3-39)	< 0.001
Fever persisted at 4th day	100 (52.91)	13 (92.86)	0.004
Total parenteral nutrition	0	1 (7.14)	0.069
Serum albumin, g/dL	3.9 (2.2-5.0)	3.6 (2.0-4.5)	0.114
Prolong broad antibiotic	116 (61.38)	11 (78.57)	0.259
Current steroid use	3 (1.59)	1 (7.14)	0.250
Septic shock	30 (15.87)	4 (28.57)	0.260
Sites of infection			
Blood	48 (25.40)	4 (28.57)	0.758
Catheter	1 (0.53)	1 (7.14)	0.133
URI	16 (8.47)	1 (7.14)	0.999
LRI	39 (20.63)	10 (71.43)	0.001
Abdominal	7 (3.70)	0	0.999
UTI	10 (5.29)	0	0.999
Skin, soft tissue	33 (17.46)	1 (7.14)	0.473
Anal area	7 (3.70)	0	0.999
Unknown	65 (34.39)	1 (7.14)	0.039
Pathogens*			
Gram positive	22 (11.70)	3 (21.43)	0.389
Gram negative	61 (32.45)	7 (50.00)	0.240
Fungus	22 (11.64)	7 (50.00)	0.001
E. faecalis	5 (2.65)	1 (7.14)	0.352
S. viridians	5 (2.65)	0	0.999
E. coli	21 (11.11)	0	0.370
Klebsiella	9 (7.56)	1 (20.00)	0.348

Aspergillus	15 (7.94)	4 (28.57)	0.030
Candida	7 (3.70)	3 (21.43)	0.024
Galactomannan positive	24 (12.70)	3 (21.43)	0.406
ICU stay, days	7 (1-38)	8 (2-20)	0.679
Hospital stay, days	28 (2-102)	25 (6-65)	0.897

Note. Data presented as median (range) for numerical variables and number (percentage) for categorical variables; AML: Acute myeloid leukemia; APL: Acute promyelocytic leukemia; ALL: Acute lymphoblastic leukemia; BM: bone marrow; I3A7: Idarubicin 3 days plus Ara-c 7 days; I2A5: Idarubicin 2 days plus Ara-c 5 days; G-CSF: Granulocyte colony-stimulating factor; URI: upper respiratory tract infection; LRI: lower respiratory tract infection; UTI: urinary tract infection; * indicated two most common pathogens in each category; ICU: intensive care unit.

Table 2. Factors associated with mortality in acute leukemia patients with febrile neutropenia

Factors	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
AML	0.393 (0.130, 1.181)	0.249 (0.045, 1.371)
FN at admission	1.674 (0.450, 6.227)	7.843 (0.939, 65.508)
GCSF	0.695 (0.210, 2.302)	4.371 (0.597, 31.976)
Prolong broad spectrum antibiotics	0.784 (0.261, 2.353)	0.285 (0.054, 1.482)
Septic shock	2.120 (0.623, 7.205)	7.461 (1.101, 50.524)
Lower respiratory tract infection	9.615 (2.861, 32.305)	11.198 (1.822, 68.818)
Aspergillosis	4.640 (1.298-16.586)	6.631 (0.821, 53.520)

Note. AML: Acute myeloid leukemia; G-CSF: granulocyte colony-stimulating factor.

Table 3. Pathogens in acute leukemia patients with febrile neutropenia categorized by lower respiratory tract infection (LRI)

Factors	Non-LRI n = 153	LRI n = 49	p value
Gram positive	16 (10.46)	9 (18.37)	0.210
Gram negative	39 (25.49)	29 (59.18)	< 0.001
Fungus	13 (8.44)	16 (32.65)	< 0.001
E. coli	21 (13.64)	0	0.003
Klebsiella	6 (6.00)	4 (16.67)	0.101
Aspergillus	7 (4.55)	12 (24.49)	< 0.001
Candida	6 (3.90)	4 (8.16)	0.258

tract infection (**Table 3**). The lower respiratory tract infection group had higher proportions of Gram negative and fungus than the non-lower respiratory tract infection group; specifically *E. coli* (p 0.003), and Aspergillus (P < 0.001). There was no significant difference on pathogen by septic shock (**Table 4**).

Discussion

The mortality rate of acute leukemia patients with FN in this study was 6.89%. This mortality rate was lower than the previous report (32%) [3]. These differences may be due to different study population. This study included only acute leukemia patients, while the previous study enrolled cancer patients presenting at the Emergency Department; not specific to acute leukemia. These differences may imply that FN in other cancer types may be more severe. A smaller study from Brazil (110 patients) with a comparable proportion of AML patients (67.3% vs 64.03% in this study) found that the mortality rate was also higher than in this study (59%). The higher mortality rate in the Brazilian study was due to its more severe enrollment criteria. Only those admitted to the hematological ICU were enrolled [9].

There were two independent predictors for mortality in adult patients with acute leukemia and FN: lower respiratory tract infection and septic shock (**Table 2**). Lower respiratory tract infection was the strongest predictor and overcame other factors including pathogens or types of leukemia (**Table 2**). The previous study also found that pulmonary infiltration had adjusted odds ratio of 3.45 (95% CI 1.48, 8.07) for mortality in cancer patients with FN [3]. Other sites of infection were not different between the survival and death group such as hematogenous, catheter-related, or UTI. These data may imply that lower respiratory tract infection may be related to mortality than other sites of infection as previously reported [11,

Table 4. Pathogens in acute leukemia patients with febrile neutropenia categorized by septic shock

Factors	No septic shock n = 169	Septic shock n = 34	p value
Gram positive	21 (12.50)	4 (11.76)	0.999
Gram negative	57 (33.93)	11 (32.35)	0.999
Fungus	26 (15.38)	3 (8.82)	0.426
E. coli	16 (9.47)	5 (14.71)	0.359
Klebsiella	9 (8.74)	1 (4.76)	0.999
Aspergillus	18 (10.65)	1 (2.94)	0.209
Candida	8 (4.73)	2 (5.88)	0.676

12]. The mortality rate was higher in FN patients with pneumonia than those with primary bacteremia (56.4% vs 12.5%) and hazard ratio for mortality of 25.905 (95% CI 1.381, 507.006). Pneumonia was also previously shown to be associated with mortality in ALL children with adjusted odds ratio of 4.087 (p 0.028) [13].

Note that the unknown sites of infection were higher in the survival group than the death group significantly (34.39% vs 7.14%; p 0.039). These information may indicate two meanings; 1) the survival group may not have real infection or infection was not serious and 2) patients had a high chance of mortality despite identified sites of infection or infection was so serious and obviously identifiable. Even though age was previously reported to be related with mortality as well as other factors [2, 12, 14, 15], it was not strong enough to be an independent factor compared with the lower respiratory tract infection and did not remain in the final model.

Regarding the pathogen, fungal infection was significantly higher in the death group than the survival group for both Aspergillus and Candida (**Table 1**). These two pathogens were also had higher prevalent in the lower respiratory tract infection in the death group (**Table 3**). Aspergillus and Candida were reported to be the two most common invasive fungal infection in patients with hematologic malignancies without FN [16-18]. Out of 538 cases, Aspergillus accounted for 310 cases (57.62%), while Candida was found in 175 cases (32.53%) [16]. The mortality rates of Aspergillus and Candida infection were 42% and 0.5%. The mortality rates of both pathogens in this study were different from the previous study at 21.05% and 30%, respectively (**Table 1**). This study included

only FN may make different mortality rates from the previous study. Even though the mortality rate of Candidiasis in this study was higher than Aspergillosis. Aspergillosis may be a stronger factor than Candidiasis due to more pulmonary involvement (**Table 3**).

A previous report found that Gram-positive bacteria accounted for 55% in acute leukemia with FN patients [19] which was higher than this study (26%) as shown in **Table 3**. These differences may be due to different source of bacteremia. The previous study conducted in only blood stream infection, while this study included all sites of infection. However, the common Gram negative organisms were similar to previous report from China [20] that found *E. coli* and *Klebseilla* as the two most common Gram negative organisms (40% and 20%) as in this study but different from the Spanish study [19]. Once again, different sites of infection may be an explainable reason. Note that both *E. coli* and Klebsiella in this study were more prevalent in the survival group than the death group as well as in lower respiratory tract infection (*E. coli* only). It may imply that these Gram negative organisms may be susceptible or treatable. Note that septic shock was a significant predictor as previously reported [11] regardless of types of organism in this study. The mortality group had significant higher proportion of septic shock than those who survived (86.4% vs 13.6%; p < 0.001) [11]. These results may imply that septic shock with any organisms may increase mortality rate.

Presence of septic shock was another predictor for mortality in acute leukemia with FN. This factor was previously reported in those with hematologic malignancy in both children and adults [5, 21]. A study in 206 adult patients with hematologic malignancy patients (71 patients with acute leukemia or 34.5%) found that those requiring vasopressor therapy associated with ICU mortality, 30-day and 60-day mortality with odds ratio of 3.73 (P < 0.001), 2.21 (p 0.036), and 2.14 (p 0.047). Note that FN was accounted for 56.8% of the total study population [5]. Another study with 20 patients with AML and bacteremia also found that pulmonary infiltration was associated with septic shock (odds ratio of 17; p 0.001) but not mortality which may be due to small sample size [22].

There are some limitations in this study. First, this was a single site, university hospital level. Second, there were some missing data due to retrospective study design. Finally, some factors were not studied such as CRP or procalcitonin level. This study however focused on clinical factors predictive of mortality which may be more available.

We found two independent predictors of mortality in acute leukemia patients with FN: septic shock and lower respiratory tract infection regardless of leukemia type or pathogen. E. coli and Aspergillus were more common in those with lower respiratory tract infection than those without. No specific pathogens were found in cases of septic shock.

Disclosure of conflict of interest

None.

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