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Original Article

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The Outcome of Fungal Pneumonia with Hematological Cancer

Esma Eren [1], **Emine Alp** [2], **Fatma Cevahir** [3], **Tuğba Tok** [4], **Ayşegül Ulu Kılıç** [4], **Leylagül Kaynar** [5], **and Recep Civan Yüksel** [6]

[1]Kayseri City Hospital, Infectious Disease Clinic, Kayseri, Turkey
[2]Ministry of Health, Ankara, Turkey
[3]Unıversıty of Sakarya Applıed Scıences, Akyazı Vocational School of Health Services, Medical Services and Techniques Department, Sakarya, Turkey
[4]Erciyes University, Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, Kayseri, Turkey
[5]Erciyes University, Faculty of Medicine, Department of Internal Medicine, Hematology, Kayseri, Turkey
[6]Kayseri City Hospital, Intensive Care Unit, Kayseri, Turkey

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Corresponding Author:
Esma Eren, MD
Infectious Diseases Clinic, City Hospital, Kayseri, Turkey.
Tel: +90-5545965092
E-mail: esmaereneryilmaz@gmail.com

ORCID iDs
Esma Eren
https://orcid.org/0000-0002-2712-9694
Emine Alp
https://orcid.org/0000-0003-0189-6008
Fatma Cevahir
https://orcid.org/0000-0002-4834-5046
Tuğba Tok
https://orcid.org/0000-0002-9628-8197
Ayşegül Ulu Kılıç
https://orcid.org/0000-0002-4454-374X
Leylagül Kaynar
https://orcid.org/0000-0002-2035-9462
Recep Civan Yüksel
https://orcid.org/0000-0003-4496-9473

ABSTRACT

Background: Fungal pneumonia is a common infectious complication of hematological cancer (HC) patients. In this retrospective study, the objective was set to identify the risk factors and outcome of fungal pneumonia in adult HC patients.
Materials and Methods: This retrospective study was conducted with adult (>16 years) HC patients from January 2017 and December 2018.
Results: During the study period, of 181 patients included 76 were diagnosed with fungal pneumonia. The most common HC was identified as acute myeloid leukaemia (40%). Of the participating patients, 52 (29%) were hematopoietic stem cell transplant (HSCT) recipients. The median age of patients with fungal pneumonia was significantly greater: 57 *vs.* 48 (odds ratio [OR]: 1.08) and they had longer hospitalization durations (OR: 1.14). Overall, 37 patients (20%) died, and 28-day mortality was significantly greater among patients with fungal pneumonia than without fungal pneumonia (33% *vs.* 11%). The most significant risk factors for mortality in fungal pneumonia were identified as need of intensive care unit (ICU) (OR: 191.2, P <0.001) and the need of vasopressor support (OR:81.6, P <0.012). ICU-mortality was (88%).
Conclusion: Fungal pneumonia is a lethal complication in HC patients. Intensive care need is the most important predictive factor for mortality.

Keywords: Hematological cancer; Intensive care; Fungal pneumonia

INTRODUCTION

Hematological cancer (HC) incidences are increasing worldwide, and cancer patients receive intensive chemotherapy that may cause undesirable complications [1]. Infectious complications, especially fungal pneumonia, are the most important and frequent cause of death in patients with HC [2, 3]. About one-third of leukemia patients receiving chemotherapy and 80% of hematopoietic stem cell transplant recipients have at least one episode of pneumonia, and mortality may be as high as 80% in some cases [4]. Both innate and adaptive immune functions are suppressed by the cancer itself and chemotherapeutic

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Conflict of Interest
No conflicts of interest.

Author Contributions
Conceptualization: EA, EE. Data curation: EE, TT. Formal analysis: EE, FC. Funding acquisition: EE, EA, AUK. Investigation: RCY. Methodology: EA, EE, FC. Project administration: EE. Resources: EE, AUK, RCY. Software: RCY. Supervision: AUK, EA. Validation: EE. Visualization: EA. Writing - original draft: EE, AUK. Writing - review & editing: EE, EA.

agents. Fungal pneumonia is common in patients with hematological cancer due to mucosal damage caused by cytotoxic chemotherapies and steroids, neutropenia and leukocyte defects, hematopoietic stem cell transplantation (HSCT) and subsequent immunosuppressive agents used for the treatment of graft versus host disease (GVHD) [5].

The diagnosis of pneumonia in HC patients may be difficult due to fuzzy clinical and radiological signs. In HC patients, early administration of antimicrobials is critical for survival [6, 7]. This study aimed to evaluate of the risk factors and prognosis of fungal pneumonia in HC patients.

MATERIALS AND METHODS

This retrospective study was performed in a tertiary referral hospital in 1,300-bed capacity. The hematology department has a 38-bed capacity, and HSCT unit has a 37-bed capacity. All types of adult hematological cancer patients are treated at the hematology unit, and autologous and allogeneic HSCT is performed in HSCT center.

1. Patients

All HC patients consecutively hospitalized into the hematology unit and HSCT hospital between January 2017 and December 2018 were screened. Patients with fungal pneumonia were included in the study. Patients who had no infection were included as the control group.

Patients' data on infection were recorded from the infection control committee data and hospital data processing system. The demographic and clinical condition of patients; comorbidities, type of HC, the status of HC (new diagnosis, refractory, recurrence, remission), neutropenia and duration, infection episodes and antibiotics used in the last three months, prophylactic agents, were recorded from hospital electronic patient registration system.

During the study period, the patients were evaluated in two groups as fungal pneumonia and non-pneumonia group. The patients who developed fungal pneumonia were also grouped as survivors and non-survivors. The factors affecting 28-day mortality were also evaluated in this study. The patients are grouped according to their need of mechanically ventilator and vasopressor agent. The mortality is calculated for each group.

2. Definitions

In the present study, Invasive Pulmonary Aspergillosis (IPA) was defined according to The European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) criteria [8]. IPA was categorized as proven, probable or possible IPA. In our center, galactomannan is tested weekly.

An multi drug resistant (MDR) characteristic was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [9]. In the present hematology center, patients are screened weekly for rectal bacterial colonization with a rectal swab sample.

The Sequential Organ Failure Assessment (SOFA) score is the organ failure score consisted of organ system function variables. The higher score indicates the higher severity of organ system failure [10].

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Definitions of sepsis, septic shock and organ dysfunctions were used from The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [10, 11].

The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system is the severity of disease classification system. It uses 12 different physiological factors to evaluate critically ill patients within their first 24 hours of admission to the intensive care unit (ICU) [12].

3. Ethics

This research was approved by the Non-invasive Clinical Research Ethics Committee of Erciyes University (Date: 07.07.2017 No: 2017/358). The need for patient consent was waived due to the retrospective nature of the study.

4. Statistical analysis

The collected information was processed using version by 22.0 of the Statistical Package for Social. The Shapiro-Wilk test was performed to check the normality assumption of the data. The Mann-Whitney *U*-test was used for the comparison of continuous variables. Variables that *P*-value ≤0.05 were included in the multivariate logistic regression analysis. A second analysis was also conducted to determine risk factors for mortality in patients with fungal pneumonia. Similarly, values with $P \leq 0.05$ were taken in multivariate analysis. A power analysis program was used to calculate the post hoc power analysis. It was done considering fungal pneumonia as a primary outcome measure. It was determined that the study was designed to have 81% power to detect in pneumonia scoring between both groups.

RESULTS

A total of 181 adult patients with HC were included in the study, 76 (42%) of them were diagnosed with fungal pneumonia.

Clinical characteristics of the patients are provided in **Table 1**. The median age (min-max) was 53 (18-87) years and 60% of participant patients were male. The most frequent comorbidity was diabetes mellitus (20%). The most common HCs were acute myeloid leukemia (AML) (40%), acute lymphoblastic leukemia (ALL) (11%) and multiple myeloma (MM) (11%). Of the participating patients, 70 (41%) were in remission, and 19 (25%) were in relapse. Again, of the participating patients, 53 (29%) were HSCT recipients, and 29 of the recipients had allogeneic HSCT.

28-day mortality rate was 20% in all patients, 33% in the fungal pneumonia group and 11% in the non-pneumonia group.

1. Risk for fungal pneumonia

The groups with/without fungal pneumonia were compared, the risk factors for the fungal pneumonia are provided in **Table 1**.

In the patients with fungal pneumonia; the median age (range) was 57 (18 - 84) years and 60% of participant patients were male. In univariate analysis; the median age of patients with fungal pneumonia was higher than the non-pneumonia group (odds ratio [OR]: 1.08, $P = 0.02$). The duration of neutropenia and hospital stay were longer in the pneumonia group. Neutropenia was present in 80% of those with fungal pneumonia and 53% of those

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without pneumonia ($P = 0.001$). Chronic obstructive pulmonary disease (COPD) (12% *vs.* 4%), previous using prophylactic posaconazole (38% *vs.* 13%) and acyclovir (10% *vs.* 4%), febrile neutropenia episode in the past three months (39% *vs.* 11%), prior use of piperacillin/tazobactam (79% *vs.* 15%) or amikacin (41% *vs.* 4%) were also higher in the group with fungal

Table 1. Risk factors of pneumonia in hematological cancer patients

	Pneumonia (n = 76), n (%)	No Pneumonia (n = 105), n (%)	*p* value	Multivariate Analysis	
				OR (95% CI)	*p* value
Age median (min-max)	57 (18 - 84)	48 (18 - 87)	0.020	1.08 (1.04 - 1.13)	0.001
Male gender	46 (60)	62 (59)	0.482		
Neutropenia	61 (80)	56 (53)	0.001		
Neutropenia duration before pneumonia median (min-max)	11 (4 - 40)	10 (3 - 21)	0.048		
Duration of hospitalization median (min-max)	35 (15 - 120)	16 (5 - 76)	0.001	1.14 (1.09 - 1.20)	0.001
Comorbidities					
Diabetes Mellitus	20 (26)	17 (16)	0.133		
Chronic Obstructive Pulmonary Disease	9 (12)	4 (4)	0.046	28.17 (3.11 - 255.21)	0.003
Congestive Heart Failure	7 (9)	6 (6)	0.369		
Chronic Renal Disease	7 (9)	6 (6)	0.395		
Hematological Cancer diagnosis					
Acute Myeloid Leukomia	35 (46)	37 (35)	0.167		
Multiple Myeloma	7 (9)	13 (12)	0.633		
Acute Lymphoblastic Leukemia	9 (12)	11 (10)	0.716		
Myelodysplastic Syndrome	6 (8)	4 (4)	0.235		
Hodgkin Lymphoma	3 (4)	6 (6)	0.736		
Non-Hodgkin Lymphoma					
Diffuse Large Cell	3 (4)	13 (12)	0.088		
Mantle Cell Lymphoma	3 (4)	3 (3)	0.382		
Low-Grade Lymphoma	2 (2)	1 (1)	0.573		
Follicular Lymphoma	2 (3)	1 (1)	0.394		
Marginal Zone Lymphoma	-	2 (2)	0.955		
Other	6 (8)	14 (12)	0.140		
Disease status					
New diagnosis	17 (22)	19 (18)	0.572		
Relapse	19 (25)	24 (23)	0.252		
Refractory disease	9 (12)	21 (20)	0.162		
Remission	31 (41)	39 (37)	0.645		
Hematopoietic Stem Cell Transplantation (HSCT)	22 (29)	30 (29)	0.956		
Allogenic HSCT	14 (18)	15 (14)	0.465		
Autologous HSCT	8 (10)	16 (15)	0.385		
Graft Versus Host Disease	6 (8)	12 (11.4)	0.433		
Hematological Cancer Treatment					
Steroid	22 (29)	25 (24)	0.493		
Monoclonal antibody	11 (14)	14 (13)	0.826		
Chemotherapy in the past 3 months	46 (60.5)	76 (72.4)	0.109		
Remission induction treatment					
7/3 Chemotherapy protocols	14 (18)	11 (10)	0.134		
FLAG	14 (18)	13 (12)	0.260		
GMALL induction	1 (1)	6 (6)	0.130		
HOLZER	1 (1)	3 (3)	0.213		
Hyper CVAD	4 (5)	2 (2)	0.403		
Toronto	2 (2.6)	6 (5.7)	0.471		
Consolidation					
High dose ARA-C	7 (9)	8 (8)	0.701		
Previous use of antimicrobials for *prophylaxis*					
Fluoroquinolones	29 (38)	24 (23)	0.052		
Trimethoprim-sulfamethoxazole	17 (22)	12 (11)	0.064		
Fluconazole	19 (25)	15 (14)	0.083		
Posaconazole	29 (38)	14 (13)	0.001		
Voriconazole	1 (1)	3 (3)	0.486		
Acyclovir	7 (10)	5 (4)	0.001		

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Table 1. (Continued) Risk factors of pneumonia in hematological cancer patients

	Pneumonia (n = 76), n (%)	No Pneumonia (n = 105), n (%)	*p* value	Multivariate Analysis	
				OR (95% CI)	*p* value
Previous use of antimicrobials for treatment	68 (90)	42 (40)	0.001	9.76 (1.71 - 55.61)	0.010
Piperacillin/tazobactam	60 (79)	16 (15)	0.001	6.48 (1.51 - 27.87)	0.012
Meropenem	14 (18)	15 (14)	0.281		
Amikacin	31 (41)	4 (4)	0.001		
Tigecycline	4 (5)	8 (8)	0.566		
Colistin	3 (4)	5 (5)	0.792		
Moxifloxacin	12 (16)	8 (8)	0.096		
Voriconazole	8 (10)	4 (4)	0.127		
Other therapies					
Granulocyte	21 (28)	13 (12)	0.012		
GM-CSF	60 (79)	56 (53)	0.001		
A previous infectious episode in 3 months	60 (79)	42 (40)	0.001	8.33 (1.44 - 48.24)	0.018
Febrile Neutropenia	39 (51)	11 (10)	0.001		
Urinary Tract Infection	2 (2.6)	2 (1.9)	0.560		
Pnemonia	14 (18)	13 (12)	0.180		
Soft Tissue Infection	1 (2)	1 (1)	0.665		
Other	4 (5)	5 (5)	-		
Rectal colonization					
Vancomycin-resistant enterococcus	17 (22)	10 (9)	0.020		
Carbapenem-resistant *Enterobacteriacea*	15 (19)	7 (7)	0.011		

OR, odds ratio; CI, confidence interval; 7/3 Chemotherapy, 7 days of standard-dose cytarabine/3 days of an anthracycline; FLAG, fludarabine/high-dose cytarabine/granulocyte colony-stimulating factor; GMALL, German multicenter study group for adult ALL protocol; CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone ± Methotrexate/Cytarabine; ARA-C, Cytarabine; GM-CSF, Granulocyte-macrophage colony-stimulating factor.

pneumonia. Numeric data and table number were added. Rectal colonization with MDR bacteria was more common in the fungal pneumonia group (**Table 1**).

However, in multivariate analysis; the significant risk factors for fungal pneumonia were identified as; age (57 *vs.* 48) (OR: 1.08), median duration of hospitalization (35 days *vs.* 16 days (OR:1.14, P <0.001), Chronic obstructive pulmonary disease (COPD) (OR: 28.17, P = 0.003), previous use of antibiotics (OR: 9.76, P <0.001) and previous episode in past three months (OR: 8.33) and previous use of piperacillin/tazobactam (OR: 6.48, P = 0.012).

2. Outcome of Fungal pneumonia

The Incidence of death was observed in 25 (33%) patients with fungal pneumonia. The risk factors of mortality in HC patients with fungal pneumonia are provided in **Table 2**. Twenty-three patients were transferred to ICU, 16 patients were mechanically ventilated, four patients received high flow oxygen therapy, and three patients received nasal oxygen therapy. ICU-mortality was observed in 86% of the patients. Mortality risk was higher in patients who needed for respiratory care (mechanical or non-invasive ventilation) or oxygen supplementation. Lactate levels >2 mmol/L, APACHE II (26 *vs.* 14) score and SOFA of >6 on infection day and complications of fungal pneumonia; acute respiratory distress syndrome (ARDS), septic shock and MODS were associated with high mortality (P <0.05). Patients in need of intensive care due to sepsis, septic shock or multi organ dysfunction syndrome (MODS) were evaluated according to prognosis provided in **Table 3**. Accordingly, 15 patients supported by both vasopressor and mechanical ventilator died. The mortality rate was 57% in patients receiving only vasopressor support, 33% in patients receiving only mechanical ventilation (**Table 3**).

In multivariate analysis; the necessity of mechanically ventilation (OR: 191.22) and vasopressor support (OR: 2.07 - 79.6, P <0.001) were considered as a risk factor for mortality remission of the hematological cancer was seen as a mortality reducing factor (P = 0.01).

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Table 2. Risk factors of mortality in pneumonia patients

	Non-survive patients (n = 25), n (%)	Survive patients (n = 51), n (%)	*p* value	Multivariate analysis	
				OR (95% CI)	*p* value
Age median (range)	58 (21 - 76)	56 (18 - 84)	0.678		
Male gender	18 (72)	28 (55)	0.152		
Neutropenia	19 (76)	42 (82)	0.549		
Neutropenia duration before pneumonia median (range)	11 (4 - 33)	10.5 (4 - 40)	0.306		
Comorbidities					
Diabetes mellitus	5 (20)	15 (29)	0.422		
Chronic obstructive pulmonary disease	4 (16)	5 (10)	0.465		
Congestive heart failure	2 (8)	5 (10)	0.798		
Chronic renal disease	4 (16)	3 (6.0)	0.209		
Disease status					
New diagnosis	8 (32)	9 (18)	0.158		
Relapse	12 (48)	7 (14)	0.001		
Refractory disease	2 (8)	7 (14)	0.468		
Remission	3 (12)	28 (55)	0.001	0.041 (0.01 - 0.78)	0.034
Hematopoietic stem cell transplantation (HSCT)	10 (40)	12 (23)	0.137		
Allogenic HSCT	7 (28)	7 (14)	0.130		
Autologous HSCT	3 (12)	5 (10)	0.769		
Graft versus host disease	2 (8)	4 (8)	0.981		
Previous use of antimicrobials for treatment	24 (96)	44 (86)	0.259		
Invasive fungal infections					
Probable invasive pulmonary aspergillosis	8 (32.0)	13 (25)	0.592		
Possible invasive pulmonary aspergillosis	15 (60)	35 (69)	0.607		
Proven invasive pulmonary aspergillosis	-	1 (2)	-		
Mucormycosis	-	2 (4)	-		
Other	-	2 (4)	-		
Intensive care need	23 (92)	3 (6)	0.001	191.22 (10.65 - 3,434.83)	0.001
APACHE II On infection date: median (range)	26 (14 - 34)	14 (7 - 29)	0.001		
SOFA median (range)	9 (1 - 14)	3 (0 - 13)	0.001		
SOFA >6	24 (67)	7 (9)	0.001		
Lactate >2mmol/l	13 (52)	5 (10)	0.001		
Mechanically ventilator	16 (64)	1 (2)	0.001		
Vasopressor support	19 (76)	3 (6)	0.001	81.68 (2.66 - 2,508.48)	0.012
Complications					
Acute respiratory distress syndrome	9 (36)	2 (4)	0.001		
Alveolar hemorrhage	3 (12)	3 (6)	0.388		
Sepsis	5 (20)	13 (25)	0.058		
Septic shock	14 (56)	3 (6)	0.001		
Multi organ dysfunction syndrome	7 (28)	-	-		

OR, odds ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment.

Table 3. Outcome of Fungal Patients Need Of Mechanical Ventilation And Vasopressor Support

Groups (n)	MV	VP	Mortality, n (%)
Group a (15)	Yes	Yes	15 (100)
Group b (7)	No	Yes	4 (57)
Group c (2)	Yes	No	1 (33)
Group d (52)	No	No	5 (9)

MV, mechanical ventilation; VP, vasopressors.

DISCUSSION

In this retrospective study, we found that; older age, longer length of stay COPD, previous infection episode and using antibiotics for infection treatment recently increase the risk of fungal pneumonia in patients with HC. In patients with fungal pneumonia, need for intensive care and vasopressor support were the most important prognostic factors.

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Previous studies reported that higher SOFA and APACHE II score on the day of infection have a poor prognosis in hematological cancer patients [13]. In a previous study, it was shown that APACHE II score of ≥25 was of poor prognosis when hematologic cancer patients needed intensive care [14]. In our results, ICU need and vasopressor support were the most important prognostic factors for mortality in HC patients with fungal pneumonia (**Table 3**). Similarly, the APACHE II score was 26 in non-surviving and 14 in surviving patients. The differences in APACHE II scores were found to be significant. Also, SOFA of >6 increases the mortality rate about 2.5 times. Based on the results of the available data, ICU and in hospital mortality rates remain high in this patient population. Reported hospital mortality is 50% and ICU mortality has ranged from 33% to 84% for patients with HM [15-19]. Present hospital mortality and ICU mortality were identified as 32% and 85%, respectively. It was concluded based on the present findings that HC patients in the intensive care unit should be supported within the framework of ethical rules.

In recent years, the treatment of hematologic malignancies has advanced considerably. The treatment also leads to a longer risk of neutropenia and a higher risk of fungal pneumonia. Neutropenia, which is usually caused by chemotherapy or radiotherapy, is a major risk factor for bacterial and fungal lung infections [5]. Similarly, in this study, the Incidence of neutropenia was found to be higher in patients with fungal pneumonia than in non-fungal pneumonia patients (80% *vs.* 53%).

In our results, longer length of stay period had a greater risk of fungal pneumonia as compared to patients with shorter hospitalization periods (35 days *vs.* 16 days).

Besides, our patients with febrile neutropenia episodes within three months were at higher risk of fungal pneumonia. Besides, the risk of fungal pneumonia was found to be increased in patients using piperacillin/tazobactam and amikacin therapy within three months. In the present center, these two agents are used in the empirical treatment of febrile neutropenia.

Based on our data, we found that patients using posaconazole prophylaxis had a higher risk of fungal pneumonia. In line with the guidelines, posaconazole is used prophylactically for patients receiving high-risk chemotherapy regimens [20]. Also, these patients were at high risk for bacterial or fungal infection. Besides, there may be reasons that prevent absorption such as mucositis. High fungal pneumonia rate was attributed to this group.

Older age is a risk factor for fungal pneumonia in HC patients. In previous studies, at an age more aged than 60 years has been found as a risk factor for fungal pneumonia and fungal pneumonia-related deaths [21, 22]. It was found in this study that older age increased the risk of fungal pneumonia by about 1.08 times in HC patients.

Although there are some limitations such as retrospective or single center in our study, it may provide valuable information because there are few reports on the Incidence, risk factors and outcomes in patients with fungal pneumonia and HC patients.

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