

Prognostic factors for survival in patients with acute invasive fungal rhinosinusitis

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ABSTRACT

Background: Acute invasive fungal rhinosinusitis (AIFR) is an aggressive opportunistic infection with a high mortality rate. There are few reports that demonstrate an improvement in the overall prognosis. Furthermore, definite prognostic factors related to patient survival remain unclear.

Objective: The objective of this study was to evaluate the various clinical factors related to survival of patients with AIFR.

Methods: This is a retrospective case series with patients treated for AIFR between 1997 and 2013. A total of 45 patients with AIFR were enrolled for analysis. We evaluated demographics, clinical characteristics, and disease course.

Results: Mean age of patients was 59.6 years. AIFR developed most commonly in patients with immunocompromised host, such as diabetes ($n = 23$) or hematologic malignancy ($n = 17$). There were two main genera of fungus, *Aspergillus* ($n = 30$) and *Mucor* ($n = 14$). Headache, cranial neuropathy, visual loss, and orbital pain were the most common presenting symptoms. Overall survival was 53%. Underlying hematologic malignancy and diabetes were significantly associated with overall survival, and accompanying severe neutropenia and elevated C-reactive protein (CRP) were also related to poor prognosis. Initial presentation with facial swelling, involvement of nasal septum, or shorter symptom duration was also associated with survival reduction. Multivariate analysis revealed that CRP more than 5.50 mg/dL (Hazard ratio [HR], 9.04; $p = .003$) was an independent prognostic factor in patients with AIFR.

Conclusions: Overall survival rate remained approximately 50% in patients with AIFR. The prognosis of AIFR is significantly influenced by underlying diseases, accompanying neutropenia, CRP levels, symptom duration, involvement of septum, and the presence of facial swelling. Elevation of CRP, in particular, was an independent predictor of poor outcomes and should be monitored appropriately.

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Acute invasive fungal rhinosinusitis (AIFR) is an aggressive infectious disease caused by invasion of fungal organisms into surrounding tissues. It is rare but considered a medical and surgical emergency, because there are many crucial structures around the nasal cavities and paranasal sinuses, such as the orbits, skull base, and cavernous sinuses. Additionally, almost all AIFR occurs in immunocompromised hosts; therefore, morbidity and mortality are very high, ranging from 20% to 80%.^{1–4} Despite development of medical and surgical therapeutic strategies for AIFR, there are few reports that demonstrate an improvement in the overall prognosis.

The most common mycological etiologies for AIFR are *Aspergillus* and *Mucor*.^{3,5,6} However, it is not easy to confirm the diagnosis of AIFR before pathologic examination because of poor culture sensitivity and nonspecific radiologic findings, such as severe unilateral mucosal thickening or bony erosion.⁷ Even pathologists cannot definitively diagnose all cases of AIFR. In 2009, a consensus group of the European Organization for Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) proposed a revised definition of invasive fungal disease (IFD). Proven, probable, and possible IFD were defined according to EORTC/MSG criteria.⁸ Because delay in treatment of AIFR can be fatal, the clinical implications of this guideline are very important, especially in the selection of empiric treatment.

Previous studies have generally included a relatively small number of cases.^{9–11} Some reports have said that the underlying diseases, such as hematologic diseases, most affect overall survival.⁵ Other authors have reported that accompanying cranial neuropathy or intracranial involvement was related to poor prognosis.³ Unfortunately, definite prognostic factors related to patient survival remain unclear. Because

of this limited evidence, there are various treatment strategies for AIFR. According to a recently published systematic review, some clinical factors are significantly associated with favorable or poor prognosis.¹² However, definitions of AIFR and selection of risk factors varied among the included studies. In this study from a single institute, clinical factors were reviewed, and their correlation with overall survival was analyzed to verify and identify prognostic factors in patients with AIFR.

MATERIALS AND METHODS

All patients treated for AIFR in the Department of Otorhinolaryngology, Head and Neck Surgery between 1997 and 2013 were included in this study. After IRB approval (SMC-2014-01-030), medical records were reviewed to obtain patient demographics and clinical characteristics, including symptoms, laboratory data, and clinical courses.

The diagnosis of AIFR was established according to EORTC/MSG criteria with clinically acute courses (less than four weeks). Proven AIFR was diagnosed through microscopic evidence of tissue invasion of fungal organisms causing tissue damage. Probable and possible cases were determined according to the guideline.

Clinical factors, including underlying diseases compromising immune status, blood laboratory levels, and symptoms at diagnosis, were obtained. The types of antifungal agents given to patients were also included for analysis. Information about fungal genus was obtained from the pathologic reports. Additionally, anatomic involvements were also established from documented surgical records. However, we decided the extent of the lesion through endoscopic exam and radiologic findings in patients without surgical intervention. The lesions were classified according to the involvement of nasal cavities and paranasal sinuses, as the way of staging malignant neoplasm. The inferior and middle turbinates were considered as the lateral nasal wall.

The primary outcome of this study was overall survival. Survival was measured from initial diagnosis of AIFR to death. Comparisons were made using the χ^2 test, independent t test, or Fisher's exact test. Univariate and multivariate analysis of prognostic factors were performed using Cox proportional hazards models. All continuous vari-

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ables were analyzed using receiver operating characteristic (ROC) curves and area under the ROC curves (AUC). Kaplan-Meier survival analysis and Log-Rank test were also used for comparison. All statistical analysis was performed using SPSS 20.0 for Windows (IBM Corp., Armonk, NY). A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 45 patients with AIFR were enrolled for analysis. Table 1 summarizes the patient demographics. The mean age of the patients was 59.6 (range, 10–80) years. According to EORTC/MSG guidelines, 37 patients were diagnosed with proven AIFR. An additional seven probable and one possible AIFR were identified. AIFR developed most commonly in immunosuppressed patients, such as those with diabetes (*n* = 23), hematologic malignancy (*n* = 17), or other causes (oral corticosteroid use, solid organ tumors, or organ transplantation). There were 13 patients with multiple causes of altered immune status and 3 immunocompetent patients.

The two main genera of fungus were *Aspergillus* (*n* = 30) and *Mucor* (*n* = 14). Both of them were identified in one case, and another case was found to have *Schizophyllum commune* by rRNA sequencing.¹³ However, there was no significant difference in pathogenic organism according to the underlying diseases. *Mucor* was identified in 8 patients among a total of 23 diabetic patients (*p* = .59) and in 5 of 17 patients with hematologic malignancy (*p* = .39). AIFR caused by *Aspergillus* similarly showed no difference according to underlying disease. A total of 15 of 23 diabetic patients (*p* = .83) and 13 of 17 patients with hematologic malignancy (*p* = .28) diagnosed with *Aspergillus*.

Clinical Features

Complete blood count, fasting glucose, erythrocyte sedimentation rate, C-reactive protein (CRP), and hemoglobin A1c levels at the time of initial diagnosis were measured and analyzed. As a result, mean hemoglobin levels were 10.8 mg/dL and mean CRP levels were elevated above the normal range (<0.3 mg/dL).

The median duration of symptom was seven days (range, 1–30). Headache (*n* = 31, 42%), cranial nerve palsy (*n* = 16, 36%), visual loss (*n* = 13, 29%), and orbital pain (*n* = 12, 27%) were common presenting symptoms (Table 1). Patients with sinonasal symptoms, such as nasal obstruction, rhinorrhea, and/or epistaxis, accounted for six (13%). Additionally, there are 3 of 45 patients (7%) who suffered from fever. The most frequent sites of involvement were the maxillary sinus and lateral nasal wall. The mean number of sites of involvement was 2.6 ± 1.7 . Extranasal extension of AIFR was included in this analysis.

We also evaluated treatment modalities, including the types of operation and antifungal agents used for AIFR. Approximately 69% (*n* = 31) of operations used an endoscopic approach. All patients except one received antifungal treatment, such as amphotericin, voriconazole, and others.

Survival Analysis

Overall survival was 53% (24/45), and disease-specific survival was 78% (35/45). Among the 21 mortality cases, there are 11 deaths caused by nondisease relating etiologies. The specific causes of death were five pulmonary infections, three septic shocks, and three progressions of underlying hematologic malignancy.

On univariate analysis (Table 2), risk factors related to overall survival were underlying hematologic malignancy (Hazard ratio [HR], 2.84; 95% confidence interval [CI], 1.29–6.77; *p* = .018), underlying diabetes (HR, 0.29; 95% CI, 0.11–0.75; *p* = .01), accompanying severe neutropenia (HR, 2.70; 95% CI, 1.15–6.37; *p* = .023), and ele-

vated CRP (HR, 1.06; 95% CI, 1.01–1.11; *p* = .01). There were other factors associated with prognosis, including symptom duration until initial diagnosis (HR, 0.88; 95% CI, 0.78–0.98; *p* = .027), facial swelling at presentation (HR, 3.33; 95% CI, 1.28–8.64; *p* = .014), and involvement of nasal septum (HR, 2.71; 95% CI, 1.15–6.41; *p* = .023). The clinical factors related with disease-specific survival were as follows: CRP more than 5.50 mg/dL (HR, 5.42; 95% CI, 1.18–24.92; *p* = .030) and involvement of septum (HR, 4.78; 95% CI, 1.44–15.89; *p* = .011).

The levels of CRP were significantly higher in nonsurvivors group. The result of ROC analysis for prediction of outcome is presented in Fig. 1. It shows statistical significance (AUC 0.772, *p* = .002). At the cutoff value of 5.50, the sensitivity and specificity were 85.7% and 75.0%, respectively. The positive predictive value and negative predictive value were 75.0% and 85.7%.

Multivariate analysis showed CRP more than 5.50 mg/dL (HR, 9.04; 95% CI, 2.09–39.10; *p* = .003) as an independent, negative prognostic factor in patients with AIFR (Table 3). There was no statistical significance in multivariate analysis for disease-specific survival.

DISCUSSION

AIFR is a rare disease in healthy populations, but the clinical course of this opportunistic infection is very aggressive and results in high mortality in immunocompromised patients. Patient populations at risk include individuals with hematologic malignancies, diabetes mellitus, systemic steroid therapy, and many other conditions causing alterations in the immune system.^{1,3,14} AIFR is characterized by invasion of fungus into the mucosa, submucosa, and typically vessels of the nose and paranasal sinuses that causes tissue necrosis in adjacent organs.¹⁵ Despite increased awareness of the importance of early AIFR diagnosis in immunocompromised patients, recent reports still show a high mortality rate from 20% to 80%.^{1–3}

We evaluated how clinical variables in AIFR affected overall survival, instead of disease-specific survival, because there are many combined diseases responsible for the compromised immunity in these patients. Additionally, amphotericin, which is one of the antifungal agents of choice for AIFR, frequently causes major organ toxicity. This is one important reason for the worsening clinical course of AIFR. Treatment of the underlying disease may be postponed due to amphotericin toxicity. Furthermore, the drug itself may cause mortality. For these reasons, we insist that overall survival, rather than disease-specific survival, is more important for the estimation of actual outcomes in patients with AIFR.

The two common fungal genera that cause AIFR are *Aspergillus* and *Mucor*. Both organisms infect via inhalation of their spores and are ubiquitously found in the ordinary environment. Previous reports revealed that mucormycosis occurs more frequently in diabetic patients due to acidic and high-glucose conditions.^{10,14} However, there were no significant differences between *Aspergillus* and *Mucor* in patients with or without diabetes in this study. Furthermore, similar results were found in patients with hematologic malignancy.

Surgery and antifungal treatment with amphotericin B or other agents, such as voriconazole, are two common therapeutic strategies for AIFR. Regardless of approach, surgery is a known factor for improved survival.^{5,12} In this study, we did not find a similar result, because surgery was performed in all cases except two patients. In terms of antibiotic use, we found no statistically significant difference between the treatment and nontreatment groups. This might be because medical treatment for AIFR was conducted in all patients except one. Furthermore, there were no differences in prognosis according to the kind of antifungal drug selected.

Sinonasal symptoms and fever are the predominant symptoms of AIFR.¹⁴ In contrast to previous reports, headache, cranial nerve palsy, and visual loss were common in our patients. The majority of patients suffered from immunocompromised status, and AIFR shows the rapidly progressive and fatal course. Therefore, symptoms related to orbital involvement and other extranasal symp-

Table 1. Demographic characteristics and clinical factors associated with prognosis of acute invasive fungal rhinosinusitis

	All Patients (n = 45)	Diabetes Mellitus (n = 23)	Hematologic Malignancy (n = 17)
Age	59.6 ± 14.8	66.0 ± 8.2	56.2 ± 14.2
Sex			
Male	24 (53%)	15 (65%)	7 (41%)
Female	21 (47%)	8 (35%)	10 (59%)
Diagnosis			
Proven	37 (82%)	16 (70%)	15 (88%)
Probable/possible	8 (18%)	7 (30%)	2 (12%)
Organism			
<i>Aspergillus</i>	30 (67%)	15 (65%)	13 (77%)
<i>Mucor</i>	14 (31%)	8 (35%)	4 (23%)
Others	2 (2%)	1 (4%)	0 (0%)
Blood lab			
WBC (/mm ³)	7,048 ± 6,648	9,947 ± 6,692	1,726 ± 2,558
ANC (/mm ³)	5,252 ± 5,682	7,740 ± 6,113	1,005 ± 2096
Hemoglobin (g/dL)	10.8 ± 2.5	11.6 ± 2.3	9.1 ± 2.0
Platelet (x10 ³ /mm ³)	171 ± 140	233 ± 130	46 ± 34
Fasting glucose (mg/dL)	182 ± 94	226 ± 112	151 ± 48
ESR (mm/hour) (n = 42)	65.9 ± 38.8	68.7 ± 29.8	67.2 ± 47.6
CRP (mg/dL) (n = 44)	10.1 ± 9.4	7.9 ± 9.1	12.1 ± 9.8
HbA1c (%) (n = 24)	7.9 ± 2.4	8.3 ± 2.4	6.4 ± 0.5
Initial symptoms and signs			
Symptom duration (range)	7.7 (0–30)	10.4 (1–30)	4.7 (0–15)
Headache	19 (42%)	14 (61%)	3 (18%)
Visual loss	13 (29%)	8 (35%)	3 (18%)
Orbital pain	12 (27%)	7 (30%)	5 (29%)
Periorbital swelling	8 (18%)	3 (13%)	5 (29%)
Facial swelling	6 (13%)	2 (9%)	5 (29%)
Facial pain	9 (20%)	6 (26%)	4 (24%)
Fever	3 (7%)	0 (0%)	2 (12%)
Sinonasal symptoms	6 (13%)	0 (0%)	3 (18%)
Cranial nerve palsy	16 (36%)	11 (48%)	4 (24%)
Bilateral involvement	6 (13%)	4 (17%)	1 (6%)
Anatomic subsite involvement			
Maxillary sinus	26 (58%)	15 (65%)	10 (59%)
Ethmoid sinus	16 (36%)	9 (39%)	8 (47%)
Sphenoid sinus	11 (24%)	8 (35%)	2 (12%)
Frontal sinus	1 (2%)	0 (0%)	0 (0%)
Lateral nasal wall	24 (53%)	13 (57%)	2 (12%)
Septum	16 (36%)	9 (39%)	6 (35%)
Nasal floor	2 (4%)	2 (8.7%)	0 (0%)
Total numbers	2.6 ± 1.7	3.0 ± 1.7	2.4 ± 1.7
Extension of disease			
Orbit	10 (22%)	8 (35%)	3 (18%)
Intracranial	13 (29%)	9 (39%)	2 (12%)
Other extranasal	8 (18%)	6 (26%)	1 (6%)
Surgical approach			
Endoscopic	31 (69%)	17 (94%)	10 (59%)
External	12 (27%)	6 (26%)	5 (29%)
No surgery	2 (4%)	0 (0%)	2 (12%)
Medical treatment			
Amphotericin	42 (93%)	21 (91%)	16 (94%)
Voriconazole	17 (38%)	9 (39%)	6 (35%)
Other	2 (4%)	0 (0%)	1 (6%)
Survival			
Alive	24 (53%)	17 (74%)	5 (39%)
Dead	21 (47%)	6 (26%)	12 (71%)

WBC = white blood cell; ANC = absolute neutrophil count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HbA1c = hemoglobin A1c.

toms, such as facial pain, cranial nerve palsy, and any skin lesion, can be also present. We found that shorter duration of symptoms before diagnosis was related to worse overall survival ($p = .027$).

Early diagnosis of AIFR is crucial for successful treatment, because the fungal load may be lower in the early phases of AIFR. Additionally, suspicion for AIFR allows for prompt surgical interven-

Table 2. Univariate analysis of factors associated with overall and disease-specific survival

	Overall Survival		Disease-Specific Survival	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age	0.99	0.542	0.99	0.967
Sex, Male	0.86	0.735	1.26	0.693
Diagnosis, proven	5.32	0.103	29.28	0.270
Organism				
<i>Aspergillus</i>	1.23	0.666	0.45	0.170
<i>Mucor</i>	1.10	0.844	2.65	0.092
Underlying diseases				
Hematologic malignancy	2.84 (1.20–6.77)	0.018	2.08	0.206
Diabetes mellitus	0.29 (0.11–0.75)	0.010	0.53	0.284
Corticosteroid	1.75	0.370	2.30	0.284
Lymphoma	1.05	0.950	0.93	0.941
Solid organ tumor	0.85	0.825	0.42	0.440
Organ transplantation	0.72	0.749	0.46	0.587
Blood lab				
Severe neutropenia	2.70 (1.15–6.37)	0.023	0.83	0.782
CRP (<i>n</i> = 44)	1.06 (1.01–1.11)	0.010	1.04	0.162
>5.50 mg/dL	6.93 (2.03–23.66)	0.002	5.42 (1.18–24.92)	0.030
Initial symptoms				
Symptom duration	0.88 (0.78–0.98)	0.027	0.93	0.260
Headache	0.45	0.100	0.55	0.331
Visual loss	1.12	0.820	1.83	0.305
Orbital pain	2.29	0.080	2.86	0.070
Periorbital swelling	1.72	0.266	1.54	0.519
Facial swelling	3.33 (1.28–8.64)	0.014	1.71	0.492
Facial pain	0.58	0.388	0.75	0.708
Fever	0.60	0.619	1.33	0.784
Sinonasal symptoms	1.92	0.420	1.97	0.384
Cranial nerve palsy	1.11	0.831	2.03	0.223
Bilateral involvement	0.71	0.645	0.62	0.649
Anatomic subsite involvement				
Maxillary sinus	0.63	0.287	1.02	0.972
Ethmoid sinus	1.83	0.167	2.69	0.091
Sphenoid sinus	1.35	0.534	3.00	0.057
Frontal sinus	8.32	0.053	10.34	0.073
Lateral nasal wall	1.38	0.467	2.00	0.259
Septum	2.71 (1.15–6.41)	0.023	4.78 (1.44–15.89)	0.011
Nasal floor	0.05	0.500	0.046	0.599
Total numbers	1.25	0.062	1.53	0.082
Extension of disease				
Orbit	0.65	0.440	0.97	0.962
Intracranial	0.83	0.709	1.19	0.772
Other extranasal	1.73	0.290	0.80	0.698
Surgical approach				
Endoscopic surgery	0.87	0.758	0.86	0.799
Medical treatment				
Amphotericin	23.2	0.358	22.83	0.506
Voriconazole	0.61	0.304	0.29	0.114

CI = confidence interval; CRP = C-reactive protein.

tion and empiric treatment using an antifungal agent.^{3,16} According to EORTC/MSG criteria, the classification of IFD is divided into proven, probable, and possible categories.⁸ The clinical implication of this guideline is an emphasis on early detection and intervention through careful consideration in patients at high risk. In this study, there was no statistically significant difference ($p = .051$) in our comparisons of the survival outcomes between the proven and probable/possible criteria groups. Additional research is needed to confirm these findings.

Severe neutropenia is defined as less than 500 absolute neutrophil counts per microliter of blood. It is considered to markedly

increase risk of infection, especially by opportunistic pathogens, such as fungi.¹⁶ The most common underlying diseases in patients with AIFR are hematologic malignancy and diabetes mellitus. In the pathogenesis of AIFR, decreased and dysregulated immune responses due to those diseases have critical roles. Our results indicate that patients with severe neutropenia have 2.70-fold increased risk of mortality ($p = .023$).

Serum CRP is frequently used as a biomarker of infection. CRP was first discovered in 1930.¹⁷ Human CRP is composed of multiple subunits of polypeptide, and it is an acute-phase protein produced by the liver in response to inflammatory cytokines. Cur-

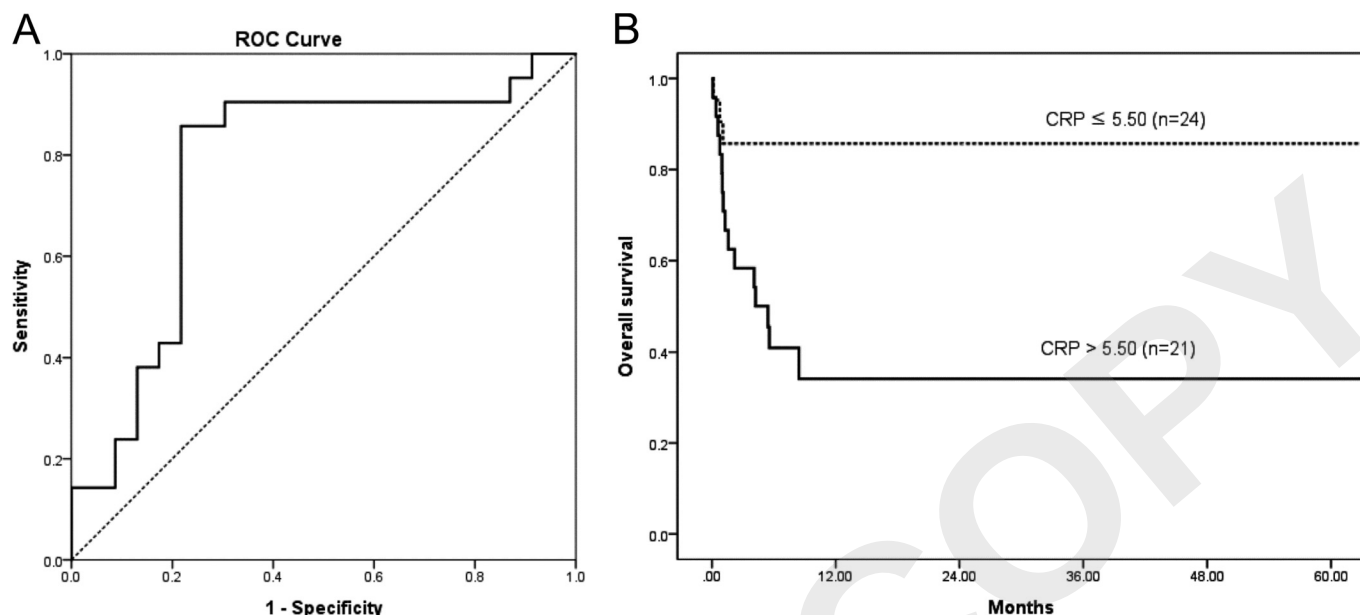


Figure 1. CRP as a prognostic factor in patients with AIFR. (A) The cutoff value of CRP with the highest sensitivity and specificity was 5.50 mg/dL ($p = .002$). (B) Survival curves according to the cutoff value of CRP in patients with AIFR ($p = .003$, Log-Rank test).

Table 3. Multivariate analysis of factors associated with overall survival

Variable	<i>p</i> -value	Hazard ratio	95% CI
Hematologic malignancy	0.105	2.56	0.66–9.97
Diabetes mellitus	0.361	0.68	0.20–2.31
CRP >5.50 mg/dL	0.003	9.04	2.01–39.10
Severe neutropenia	0.392	0.58	0.15–2.26
Symptom duration	0.102	0.87	0.74–1.04
Septum	0.483	2.20	0.79–6.11
Facial swelling	0.312	0.89	0.24–3.34

CI = confidence interval; CRP = C-reactive protein.

rently, the most widely used biomarker of systemic infection is CRP.¹⁸ AIFR is an opportunistic infection, but previous reports have shown that immunosuppression and other long-term comorbidities have no significant effect on acute-phase reactions, including elevation of CRP during severe infection.^{17–19} However, some authors suggested the limitation of CRP as a prognostic marker.^{20,21} Especially, single CRP measurement may not be reliable due to its variability. Therefore, we had collected and analyzed the repetitive measurement of CRP within one week ($n = 34$). There was a significant correlation between two CRP levels ($p < .001$, $r = 0.691$, Pearson's correlation).

Interestingly, elevated CRP levels at initial diagnosis were significantly negative prognostic factors in this study. In AIFR patients, a CRP increase of 1 mg/dL results in a 1.06-fold increase in mortality rate ($p = .01$). Therefore, we conducted ROC analysis and obtained 5.50 as a cutoff value that best predicts outcomes (AUC 0.772, $p = .002$). Multivariate Cox regression analysis has identified CRP more than 5.50 mg/dL as an independent prognostic factor of survival outcome in AIFR (HR, 9.04; 95% CI, 2.09–39.10; $p = .003$). No previous reports have suggested that CRP levels are associated with the prognosis of AIFR. This study demonstrates that CRP level should be evaluated in patients with suspicion of AIFR and can be used to direct the treatment plan.

There are limitations in this study. First, this study contains a relatively small number of AIFR patients at a single institute. However, the number of patients included in this study is comparable with previous reports, potentially due to how rare and potentially fatal the disease is. Second, we included patients with probable and possible AIFR. Unfortunately, there is no generally accepted guideline for treatment of AIFR, and some inconsistencies exist in most of the published studies. In terms of early diagnosis and intervention, we suggest that it is necessary to establish a treatment strategy for AIFR according to EORTC/MSG criteria.

CONCLUSIONS

Overall survival rate remained approximately 50% in patients with AIFR. The prognosis of AIFR is significantly influenced by underlying hematologic malignancy, diabetes, accompanying severe neutropenia, levels of CRP, duration of symptom, involvement of nasal septum, and the presence of facial swelling. Elevated clinical suspicion based on these risk factors may lead to early detection and improved treatment outcomes. Elevation of CRP, in particular, was an independent predictor of poor outcomes and should be monitored appropriately.

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