Predictive factors for invasive fungal rhinosinusitis in Diabetic Patients

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การหาตัวแปรพยากรณ์โรคinvasive fungal rhinosinusitis ในผู้ป่วยเบาหวาน

นางต่วย เพียว คัง ยุ่น

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ภูมิหลัง

ผู้ป่วยเบาหวานมีโอกาสที่จะเกิดโรคไซนัสอักสบจากเชื้อราชนิดรุกรานได้ง่ายกว่าผู้ป่วยปกติ ซึ่งอัตราการเสียชีวิตจากโรคนี้ในผู้ป่วยเบาหวานมีความหลากหลายค่อนข้างสูงในแต่ละการศึกษา

วัตถุประสงค์

เพื่อศึกษาปัจจัยที่จะทำนายอัตราการรอดชีวิตของผู้ป่วยเบาหวานที่เกิดโรคไซนัสอักสบจากเชื้อราชนิดรุกราน

วิธีการศึกษา

การศึกษาแบบย้อนหลังนี้ได้จัดทำในโรงพยาบาลระดับตติยภูมิ 4 แห่ง ในประเทศไทย, มาเลเซีย และเมียนมาร์ โดยเก็บรวบรวมข้อมูลในผู้ป่วยเบาหวานที่เกิดโรคไซนัสอักสบจากเชื้อราชนิดรุกราน ตั้งแต่ปี ค.ศ. 2008 ถึง ค.ศ.2019 ผลที่ต้องการศึกษาคืออัตราการรอดชีวิต ปัจจัยทำนายที่นำมาวิเคราะห์ ได้แก่ อายุ, ระดับฮีโมโกลบินเอวันซีในเลือด, ภาวะเลือดเป็นกรดคีโต, ระดับเม็ดเลือดขาว, ภาวะน้ำตาลในเลือดสูง, ระยะเวลาที่เป็นโรคเบาหวาน, การใช้ยารักษาเบาหวานในปัจจุบัน, ระดับครีเอทีนีนในเลือด, และการกระจายของโรคไซนัสอักสบจากเชื้อราชนิดรุกรานเข้าไปที่ตา, คาเวอร์นัสไซนัส และโพรงสมอง

ผลการศึกษา

มีการเก็บรวบรวมข้อมูลในผู้ป่วยเบาหวานที่เกิดโรคไซนัสอักสบจากเชื้อราชนิดรุกราน 65 ราย (อายุเฉลี่ย 57.9±13.4 ปี, เพศชาย 60%) ผลพบว่า อัตราการเสียชีวิตอยู่ที่ 21.5 % โดยพบว่าการกระจายของโรคไซนัสอักสบจากเชื้อราชนิดรุกรานเข้าคาเวอร์นัสไซนัส (hazard ratio 5.1, 95% CI [1.4–18.2], p=0.01) และโพรงสมอง (hazard ratio 3.4, 95% CI [1.1–11.2], p=0.05) เป็นปัจจัย[illegible]

สาขาวิชา เวชศาสตร์คลินิก ลายมือชื่อนิสิต .....

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Thwe Phyo Kan Nyunt : Predictive factors for invasive fungal rhinosinusitis in Diabetic Patients . Advisor: Assoc. Prof. ML. KORNKIAT SNIDVONGS, Ph.D.

Background: Patients with diabetes mellitus (DM) are susceptible to invasive fungal rhinosinusitis (IFRS). The mortality rate of IFRS varies greatly among the patients with DM.

Objective: To identify the prognostic factors for the overall survival of patients with DM and IFRS.

Methods: A retrospective study was conducted in four tertiary hospitals in Thailand, Malaysia and Myanmar. Patients diagnosed with IFRS and DM from 2008 to 2019 were identified. The outcome was the overall survival. Variables analyzed for risk factors were age, HbA1C level, ketoacidosis, white blood cell count, hyperglycemia, duration of DM, current use of diabetic medications, serum creatinine level, and the extensions of IFRS to the orbit, the cavernous sinus and intracranial cavity.

Results: Sixty-five diabetic patients with IFRS (age 57.9±13.4 years, male 60%) were identified. The mortality rate was 21.5%. The extensions of IFRS to the cavernous sinus (hazard ratio 5.1, 95% CI [1.4–18.2], p=0.01) and intracranial cavity (hazard ratio 3.4, 95% CI [1.1–11.3, p=0.05) predicted mortality. Current use of diabetic medications decreased the mortality risk (hazard ratio 0.2, 95% CI [0.1–0.9], p=0.03). The 6-month overall survival of the patients with and without the cavernous sinus extension were 51.4% and 83.6%, (p <0.01), with and without intracranial extension 53.3% and 88.9%, (p<0.01), and with and without current diabetic medications 82.3% and 57.5%, respectively (p=0.05).

Conclusion: The extensions of IFRS to the cavernous sinus and intracranial cavity increased the risk of death in patients with DM. Survival was primarily related to current use of diabetic medications.

Field of Study:	Clinical Sciences	Student's Signature .....
Academic Year:	2019	Advisor's Signature .....

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CHAPTER 1. INTRODUCTION

1.1 Introduction

Invasive fungal sinusitis is an aggressive and fatal infection of otorhinolaryngology. It is also high prevalence in the immunocompromised patients such as diabetes mellitus, hematological malignancy and long term corticosteroid therapy.

The clinical presentation of the disease can be quite variable but the rapid progression manner is always the same. The fever, facial pain , colored nasal discharge and orbital complaints are the most presenting and initial symptoms. Extension to the near by structures is also common , among them extension into the orbit , intracranial and cavernous sinus are most frequently seen. There are diverse group of causing fungal organism which are widely distributed in the environment. The pathogenicity of the fungus which usually occurred invasive fungal rhinosinusitis are rapid spread into the tissue and highly endothelial damage that can result as extensive necrosis and angioinvasion. Early diagnosis and prompt treatment is mandatory.

Prevalence of the Diabetes is an increasing burden of this decade. WHO projects that diabetes will be the seventh leading cause of death in 2016. (1)

Patients with Diabetes Mellitus are known to liable to infection in whole body. ENT diseases with diabetes are also increasing. There are many literatures which state that diabetic is associated prognostic factor of invasive fungal sinusitis. Diabetes ketoacidosis is one of the major complication of diabetes which can cause more rapid progression of the disease due to its hyperglycemia state and acidity.(2) But in controversies, there is literature that stated, diabetic ketoacisosis did not effect the survival outcome.(3)

Overall mortality of invasive fungal sinusitis is vary from 20 % to 80 %, with various underlying medical conditions.(4, 5) In the scope of underlying diabetes, some literature said , diabetes has higher mortality rate than other immunosuppression(6) and on the other hand diabetes survival rates is 70.58% when malignancy group is 40 % in Saedi et al .(7)

Due to strong relation in pathophysiology and immunological factors of diabetes and fungal infections, the historical belief of poor outcome in diabetes is still in a doubt. There may be some factors among diabetes with invasive fungal disease patients, which will increase fungal invasion and which can promote the survival.

However, as the association between Diabetes and Invasive fungal sinusitis has been well understood, but which factors of Diabetes contribute either in a positive or negative prognostic factor for survival are still in a debating point. There is no exact factor which can predict the prognosis of the invasive fungal disease with diabetic patients. This study will support the prediction for the prognosis of the invasive fungal rhinosinusitis with diabetes patients.

1.2 Research question

While clinical outcomes of diabetic patients with invasive fungal sinusitis are various, what factors predict favorable outcomes of these patients?

1.3 Published articles related to the thesis

1. Literature review on immune response to fungi in diabetic patients with invasive fungal rhinosinusitis
2. Predictive factors for invasive fungal rhinosinusitis in diabetic patients: systematic review and data re-analysis
3. Overall survival and prognostic factors in diabetic patients with invasive fungal rhinosinusitis in 11 years retrospective data of 3 countries

CHAPTER 2. LITERATURE REVIEW

2.1 Innate immune response to fungi in normal host

The fungal cell wall is one of the pathogen-associated molecular patterns (PAMPs) which is the first structure recognized by the immune system and activates the host immune response to the fungi. Beta-glucan is found in the fungal cell wall. Its expression on the hyphae surface is recognized and regulated by pattern recognition receptors (PRRs). These PRRs are expressed on most effector cells of the innate immune system, including on the surface of macrophages and the human monocyte derived dendritic cells. The major PRRs are Toll-like receptors (TLRs) and C-type lectin receptor, lectin-1. Cytokines and chemokine productions are induced by the signaling and receptor ligation resulting in a recruitment of innate immune cells and host antimicrobial response. The adaptive immune response is also induced.(8) *Rhizophus hyphae* induce dendritic cells which release interleukin (IL)-23 and tumor necrosis factor alpha (TNF-α). IL-23 drives T helper (Th) 17 responses and TNF-α upregulates the Th1 response. The inhibition of β-glucan receptor, Dectin-1 reduces the IL-23 production. (9)

A first line protective immune response is required to get rid of the fungal spores and limit their ability to spread before an invasive fungal infection is developed. The first line defense cells such as monocytes, macrophages and natural killer cells recognize the pathogen and kill the hyphae. The first defensive response to inhaled *Aspergillus* spores is through the monocytes that inhibit the spores germination. Monocytes are capable of ingesting *Aspergillus conidia* and inducing damage to the hyphae. The anti-

aspergillum role of CD14 + and CD16+ monocytes is against conidial germination. CD14+ and CD16+ enhance an inflammatory response by producing the TNF-α.(8) Macrophages, the next defense cells, localize the infection at the early stage and prime the adaptive immune response resulting in a more aggressive and specific response to the infection.(10) Other first line defense cells, the natural killer cells, limit tissue damage by inducing cell cytotoxicity. If the protective response of the first line defense cells is inadequate, polymorphonuclear leukocytes (PMNs) will kill the hyphae. After *Rhizopus oryzae (R. oryzae)* damages endothelial cells, the interactions between *R. oryzae* and the endothelial cells induce the phagocytosis of the fungus. (11) Neutrophils provide the rapid response that fight against fungal hyphae by infiltrating the infected site and timely apoptosis.(12)Neutrophils can induce damage to hyphae by several means. When resting spores that are highly resistant to macrophage activity(10, 12)swollen spores and hyphae are killed by non-oxidative methods and neutrophil extracellular traps (NETs) antimicrobial action kill.(8) After monocyte and neutrophil attach to fungal growth, the fungi are killed by oxidative means. PMNs activate the pro-inflammatory signaling by inducing pro-inflammatory cytokines such as TNF-α and ILs. PMNs prevent spore germination of the fungus even if the phagocytes fail to kill the spores. As a result, the mucor is non-pathogenic in healthy persons.*(13) Aspergillus hyphae* activate platelets which induce both the inflammatory (IL-8) response in monocytes and thrombin activation.(8) Platelets can adhere to the cell walls of the *Aspergillus hyphae* which limit hyphae elongation and induce damage of fungi.

2.2 Adaptive immune response to fungi in normal hosts

The T helper (Th) cells are important for the clearance of pathogenic fungi. The Th1 response plays a protective role while the Th2 response plays a non-protective role. The role of regulatory T cells (T regs) during fungal infection is to balance between the excessive inflammatory response due to the Th1 response and the hypersensitivity reaction associated with the Th2 response.(14) The Th17 response depends upon fungal loads and components to become either a protective or harmful role. The Th1 cells produce interferon gamma (IFN- γ) as a protective response against fungus. The Th17 cells produce IL-17, which has a profound impact on neutrophil activity in a fungal reaction. In addition, IL-4, IL-10 and IFN-γ are also released to fight against fungal infection.(10) An acquired immune response is mediated by the CD4 (Th1, Th2, and Th17) and CD8 T cell responses.

2.3 Immune deficiency in diabetes mellitus

The reasons why patients with diabetes mellitus are more susceptible to infections are not clearly understood. Diabetes is acknowledged as a metabolic disorder and secondary immune deficiency. Hyperglycemia is the main cause of complications such as retinopathy, nephropathy and neuropathy. It is also a precipitating factor of cardiovascular complications in long standing diabetes. Activation of a protein kinase C (PKC) isoforms, in particular PKC-B, is the well described pathway in the development of vascular complications in patients with diabetes.(15)

Innate immunity of the patients with diabetes is defective in both the humoral and cellular parts. Increased glycation status reduces the expression of class I major histocompatibility complex (MHC) on the surface of myeloid cells, and inhibits the IL-10 production by myeloid cells and the IFN- γ and TNF-α production by T cells.(16) In addition, mononuclear cells and monocytes of patients with diabetes secrete less IL-1and IL-6.(17) The hyperglycemic state also decreases vascular dilation and the NETs formation. The structure of complement is altered which inhibits complement fixation to bacteria. Complement dependent and complement independent mechanisms induced by a high level of glucose promote inflammation, proliferation and thrombosis. In diabetes mellitus, the balance between complement activation and restriction is broken.

The major effects of the above decrease phagocytosis.(15, 18)Hyperglycemia activates protein kinase C which inhibits neutrophil migration, decreases production of PMN cells, decreases chemotaxis and decreases phagocytic activity.(19) There are many studies showing the decrease of phagocytic activities. A study by Albert et al. measured phagocytic activities of the patients with type II diabetes and showed less percentage of activated macrophages when compared to the non-diabetic patients. Another study by the same group showed that the percentage of activated polymorphonuclear cells and the phagocytic activities were significantly increased after the blood glucose was well-controlled for 5 days.(10)

Patients with good metabolic control showed a robust secondary immune response to standard antigens suggesting normal T memory cell and CD4+ lymphocyte functions. In type 1 diabetes, T lymphocyte function is unaffected as long as the HbA1C is less than 8 mmol/l.(20) Nevertheless, one study showed that adaptive immunity could be

defective independent of glycaemia. There were impaired proliferative CD4+ cell responses to primary protein antigens due to an altered expression of cellular adhesion molecules and/or reduced cytokine release. Although a well-controlled blood glucose may help to normalize cell mediated immunity in diabetic patients, there are several other factors that could affect the immunity system.(21)

2.4 Immune response to fungi in patients with diabetic mellitus

Patients with DKA have elevated serum iron levels due to the release of iron from binding proteins in the presence of acidosis.(22)Iron regulates endothelial cell damage. Patients with diabetes that have endothelial damage are uniquely predisposed to developing mucormycosis, especially when the basement membrane and extracellular matrix proteins were exposed. Fungi are normal commensals in the diseased sinus area. The main infectious particles for mucormycosis are asexual spongiospores. There are three types of spores: resting spores, swollen spores, and opsonized spores. These resting spores can swell and germinate to produce fast-growing hyphae during their natural life cycle. Germination and filamentous growth within a host cause angioinvasion, vessel thrombosis, and necrosis.(23) Angioinvasion is a hallmark of zygomycotic infections. Hyperglycemia but not hyperosmolarity is responsible for the enhanced human glucose-regulated protein-78 (GRP78) expression. When endothelial cells were incubated at the pH values similar to those seen in the patients with DKA, the GRP78 expression of the endothelial cells was significantly enhanced in the lower pH values compared with the normal blood pH of 7.4.(24) The GRP78 on intact endothelial cells binds to *Mucorales* germlings. Iron and the overexpression of glucose-

induced GRP78 enhance endothelial cell susceptibility to *R. oryzae*-induced fungal invasion and damage. Of importance, the anti-GRP78 blocked this enhanced endothelial cell susceptibility to *R. oryzae*–induced damage.(24)

CHAPTER 3. RESEARCH OBJECTIVES AND HYPOTHESIS

3.1 Objectives

To identify likely prognostic factors which predict the outcomes of diabetic patient with invasive fungal rhino sinusitis

3.2 .Hypothesis

Factors related with chronic immune impairment predict poor outcomes of diabetic patient with invasive fungal rhino sinusitis. These factors are such as glucose level, neutrophil count and DKA.

CHAPTER 4. Predictive Factors for Invasive Fungal Rhinosinusitis in Diabetic Patients: Systematic Review and Data Re-analysis

4.1 Material and Methods

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. Medline, EMBASE, and Cochrane database were searched using the terms: “fung*” AND “rhinosinusitis” AND “invasive” AND “diabetes OR ketoacidosis”. The last search was performed on 30 May 2019. Inclusion criteria were case reports or case series reporting IFRS patients with original data regarding diabetic condition, the disease extension, medical and surgical treatments, and survival outcomes. Data reported by the same authors or the same institutions was checked to exclude any duplication. Articles were excluded when duplication was uncertain. Case series were excluded when the data of individual patients were not separately reported. Articles in a language other than English were excluded. Diagnostic criteria for diabetes mellitus were fasting plasma glucose values ≥ 7.0 mmol/L (126 mg/dl), a 2-hour post-load plasma glucose level ≥ 11.1 mmol/L (200 mg/dl), HbA1c ≥ 6.5% (48 mmol/mol); or a random plasma glucose ≥ 11.1 mmol/L (200 mg/ dl) with the presence of signs and symptoms.(25, 26) Diagnostic criteria for IFRS were radiological imaging and histopathological evidence of hyphal forms within the sinus mucosa, submucosa, blood vessels, or bone.(27)

Study selection was performed independently by two reviewers (TPKN and KS). The reviewers independently screened the titles and abstracts based on the predetermined eligibility criteria. The full texts of the selected articles were reviewed. Data were extracted from the included studies using a predetermined data collection spreadsheet. Six prognostic factors related to diabetes (plasma glucose level, HbA1C, ketoacidosis, leukopenia, blood creatinine level, and duration of diabetes,) and one prognostic factor related to IFRS extension (the cavernous sinus extension) were evaluated. The outcome was overall survival. Time to event was measured from the initial diagnosis of invasive fungal sinusitis to death. Univariate analysis was done for each variable. Variables with

potential risks were incorporated to multivariate analysis. Backward stepwise Cox proportional hazard model was run to assess potential hazard ratio. Kaplan Meier curve and Log-rank test were used for analyzing survival outcomes. STATA 15 was used for the data analysis. A p-value less than 0.05 was considered statistically significant.

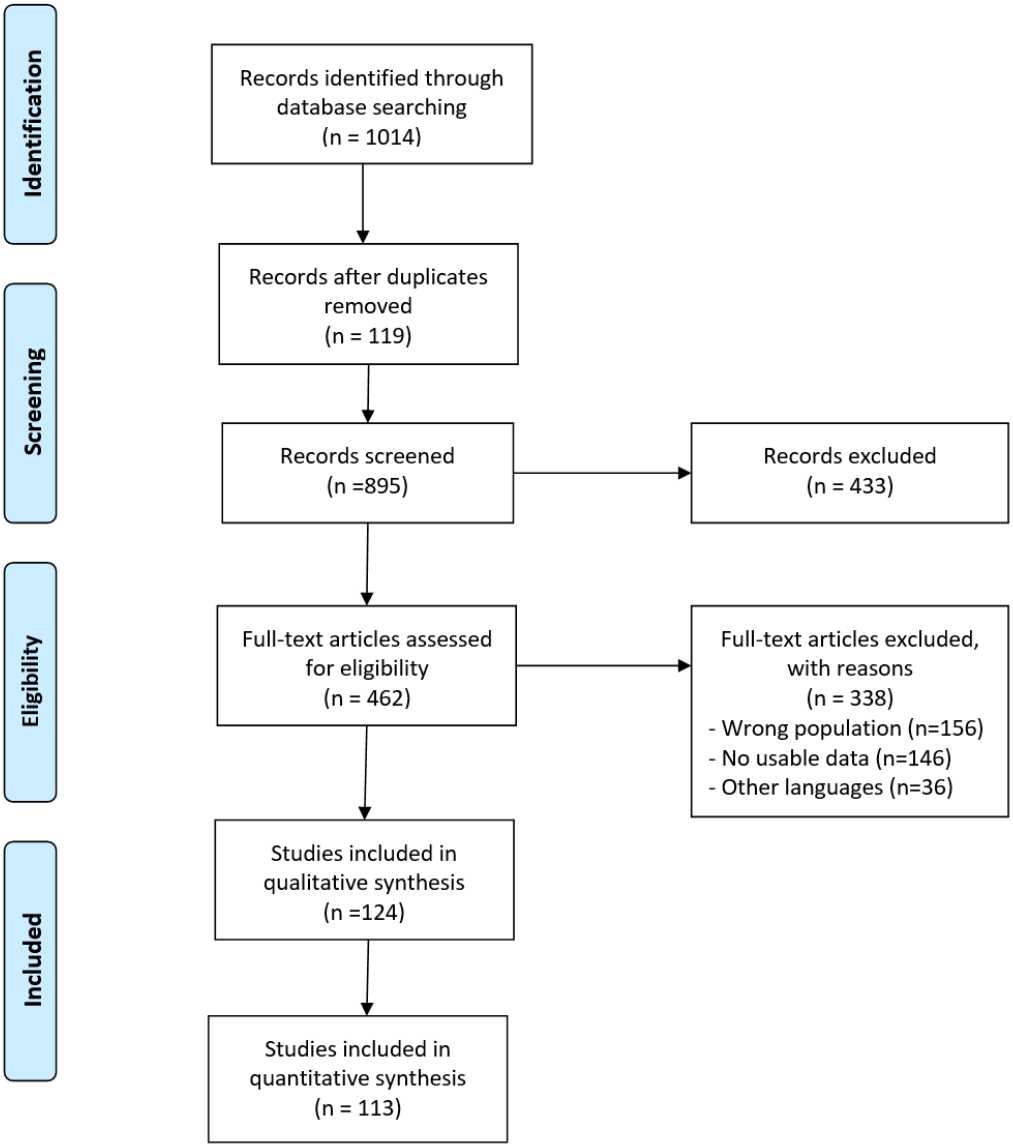


Figure 1. *Prisma flow diagram of systematic review on the selected manuscripts for analysis*

4.2 Results

Study selection

A total of 1,014 articles were identified by systematic searches. There were 119 duplicates. The titles and the abstracts of 895 studies were screened, 462 full texts were reviewed, and 338 studies were excluded after the full text review. The reasons for exclusion are listed in Figure 1. Finally, 124 studies were included for data synthesis.(28-151) A flow chart of the study retrieval and selection is presented in Figure 1.

Patients

There were 258 diabetic patients with IFRS. The mean age was 55.9 years and 55.6% were male. There was a wide geographical distribution. Most patients were from India (17%), followed by USA (16%), Korea (14%), Iran (9%) Turkey (8%), Germany (3%), Taiwan (3%) and Japan (3%). Type II diabetes was 87.2% and type I was 12.8%. Thirteen patients (5.0%) were newly diagnosed with type II diabetes at the time of admission. Most patients (71.4%) had poor glycemic control. Fifty-one patients (19.8%) had diabetic ketoacidosis.

Mucormycosis accounted for 62.9% and aspergillosis accounted for 24.2% of the IFRS patients. Three patients (1.0%) had both mucormycosis and aspergillosis. Other types of fungi such as Candida species and Absida corymbifera accounted for 3.6%. The type of fungal hyphae was not specified in 8.6% of the patients. The mean duration of symptoms was 22.7±37.6 days. Two-hundred and forty-one patients (93.4%) were diagnosed with acute IFRS and 17 patients (6.7%) were chronic IFRS. The mean duration of symptoms in acute IFRS was 12.7±15 days and chronic IFRS was 103 ±67 days. Symptoms and signs were reported in 229 patients (118 records): 152 patients (66.4%) had complaints of eye symptoms and 77 patients (33.6%) had headaches. Black eschar was the most common sign. Fourteen patients (6.1%) did not have black mucosa or necrosis. Radiological imaging was reported in 245 patients (120 records), 129 patients (52.7%) had orbital invasion and 50 patients (20.4%) had the cavernous sinus

invasion. The data from 120 records showed that 221 out of the 229 patients received antifungal treatment, 89% were treated with Amphotericin B derivatives (68% received Amphotericin B derivatives as a sole agent). Among patients who received Amphotericin B derivatives, 69% of the patients improved and survived. Eight patients did not receive antifungal treatment due to renal failure, multiorgan failure and severe medical conditions. Of the total 258 patients, 221 patients (85.6%) underwent a surgical treatment, 165 patients (63.9%) underwent endoscopic approach.

Prognostic factors and overall survival analysis

Follow-up time was reported in 207 patients (120 records). The data were used for overall survival analysis. The mortality rate was 31.8%. The mean follow-up time was 11.4 ± 18.0 months (range 0.6-120 months). Plasma glucose levels were reported in 70 patients (52 records). The mean plasma glucose level was 391.3±216.4 mg/dl and 56 patients (80%) had plasma glucose above 200 mg/dl. HbA1c levels were reported in 32 patients (21 records). The mean HbA1c was 9.7 ±2.8 and 10 patients (32%) had HbA1c greater than 11. The duration of having diabetes before admission was reported in 56 patients (44 records). The mean duration of having diabetes was 5.6±6.2 years. Nineteen patients (33%) had less than one-year duration, 21 (38%) between 1-10 years and 16 (29%) above ten years. White blood cell counts were reported in 55 patients (42 records). The mean total white blood cell count was 13,576.0 ± 8,846.5 $x10^3$ cell per liter. Six patients (10%) had a total white blood cell count less than 4,000 cell per liter, 18 (33%) had 4,000-11,000 and 31 (57%) had greater than 11,000. Serum creatinine was reported in 35 patients (24 records). The mean serum creatinine level was 1.5 ± 0.8 mg/dl. Twenty-eight patients (79%) had serum creatinine level greater than 1 mg/dl. Fifty-one patients (24.6%) had ketoacidosis. Radiological imaging was reported in 245 patients (120 records). Fifty patients (20%) had the cavernous sinus extension.

The univariable logistic regression analysis revealed that the cavernous sinus extension was a significant risk factor (hazard ratio (HR) 2.1, 95% confidence interval (CI) 1.2 to 3.6, p=0.01). As a potential risk factor, diabetic ketoacidosis was assessed using multivariate analysis together with the cavernous sinus extension. The multivariable logistic regression analysis showed that the cavernous sinus extension independently

predicted poor prognosis (HR 2.6, 95% CI 1.2 to 5.4, p=0.01). The data are displayed in Table 1. In the patients with the cavernous sinus extension, the overall survival at two months, six months and 12 months was 69.7%, 57.1%, and 43.9%, respectively. These overall survivals were significantly lower than those of the patients without the cavernous sinus extension (80.9%, 75.1% and 73.9%, respectively, p=0.01). The data are displayed in Figure 2.

Risk factors	Univariate analysis				Multivariate analysis			
	Hazard ratio	95% Confidence Interval		P-value	Hazard ratio	95% Confidence Interval		*p*-value
Age	1.00	.98	1.01	0.86	1.00	.98	1.02	0.76
Diabetes ketoacidosis	.68	.39	1.17	0.16	1.57	.72	3.43	0.26
Cavernous sinus involvement	2.09	1.2	3.6	0.01	2.56	1.21	5.40	0.01
Plasma Glucose	2.05	.61	6.96	0.25				
HbA1C	.38	.05	3.14	0.37				
Total WBC count	1.22	.55	2.72	0.62				
Creatinine	1.68	.20	14.01	0.63				
Duration of DM	1.07	.56	2.04	0.63				

Table 1. Prognostic factors on overall survival of invasive fungal rhinosinusitis in diabetic patients

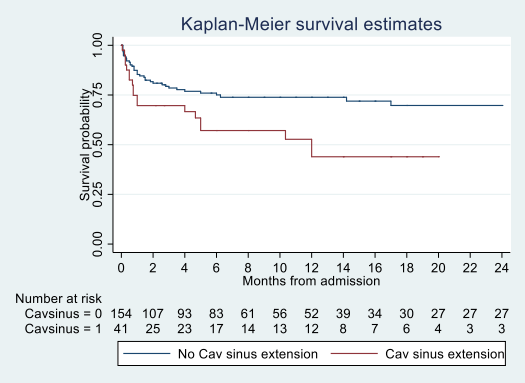


Figure 2. Overall survival of diabetic patients with invasive fungal rhinosinusitis with and without the cavernous sinus extension (systematic review)

4.3 Discussion

In this review, the mortality rate of IFRS in diabetic patients was 31.8% which was lower than the mortality rate of IFRS in the general population (50-80 %).(4, 5, 152) In line with our review, a systematic review by Turner, et al. showed that IFRS in patients with diabetes had twice the overall survival than patients with other underlying diseases.(4) When the raw data of individual case reports were pooled, our findings showed that the cavernous sinus extension was an independent factor which predicted the overall survival of diabetic patients with IFRS. Angioinvasion and vascular thrombosis caused by IFRS lead to the cavernous sinus extension. Clinical presentations may include bilateral exophthalmos, complete ophthalmoplegia, lid drop, and signs of meningeal irritation associated with spiking fevers.(153) Similar to the cavernous sinus thrombosis in acute bacterial rhinosinusitis, our review showed that the cavernous sinus extension by IFRS was fatal. The cavernous sinus is a dangerous area for endoscopic sinus and skull base surgeries due to its neurovascular structures. Therefore, the cavernous sinus extension is a hard-to-treat condition.

Although other variables also have potential risks, they are correctable resulting in more favorable outcomes. Understanding immunopathology of the underlying immunocompromised diseases and restoration of the host immune dysfunction are essential for treating IFRS together with adequate surgery and appropriate antifungal treatments. Diabetes Mellitus affects both the humoral and cellular immune responses of the innate and adaptive immune systems. The expression of class I major histocompatibility complex is impaired. The structure of complement and the balance between complement activation and restriction are altered. In poorly controlled diabetes, hyperglycemia diminishes vascular dilation and activates protein kinase C which inhibits polymorphonuclear cells production, neutrophil migration, chemotaxis and phagocytic activity.(15) Furthermore, diabetic ketoacidosis causes an overexpression of the glucose-induced glucose-regulated protein (GRP) 78 which induces endothelial cell damage and fungal invasion.(24) In addition, when acidosis is present, iron is released from its binding proteins which regulates endothelial cell damage. (22) Iron and the overexpression of glucose-induced GRP78 enhance

endothelial cell susceptibility to R. oryzae-induced fungal invasion leading to endothelial damage.(15) Germination and rapid filamentous growth of mucormycosis within the endothelial damage, the exposed basement membrane and extracellular matrix proteins cause angioinvasion, vessel thrombosis, and necrosis.(23)

IFRS is a fatal disease, therefore, neurological examination together with radiological imaging investigation should be performed to evaluate the cavernous sinus and intracranial extension. Magnetic resonance venography may be requested in specific cases for the assessment of the cavernous sinus extension. Diabetic ketoacidosis and hyperglycemic state should be assessed and treated.

The limitations of this systematic review included a retrospective nature of the included studies, and publication bias. Disadvantages of case reports and case series included missing data, confounders, and risks of bias. There were multiple factors which contributed to publication bias. Investigators commonly avoided submitting the results which were not supported by the known findings. Poor therapeutic outcomes and high mortality rate were not reported probably due to the investigators' assumption that they had made mistakes. On the other hand, publishers are not interested in the null results. In addition, most journals prefer high quality studies. Preregistered studies prior to data collection and analysis are preferred by several journals. Thus, a limited number of studies could be included.

4.4. Conclusion

Therapeutic outcomes of invasive fungal rhinosinusitis in diabetic patients are diverse. The disease extension into the cavernous sinus predicts a high mortality rate. In practice, restoration of the immune function and a total disease eradication could improve the treatment outcomes. Patients can have favorable overall survival when diabetic conditions are well controlled.

CHAPTER 5. OVERALL SURVIVAL AND PREDICTIVE FACTORS FOR INVASIVE FUNGAL RHINOSINUSITIS IN DIABETIC PATIENTS

5.1 Material and Methods

A retrospective study was conducted in three countries in Southeast Asia (Thailand, Malaysia and Myanmar). Medical records from 1 January 2008 to 31 December 2019 of four tertiary University hospitals were reviewed. This study was approved by the Institutional Review Board of all four hospitals, including (1) The King Chulalongkorn Memorial Hospital, Bangkok, Thailand (IRB number 085/62), (2) Ear, Nose, Throat & Head and Neck Surgery Hospital, Yangon, Myanmar (IRB number 184(ENT)/UMM/2018), (3) Eye, Ear, nose, Throat & Head and Neck surgery hospital, Mandalay, Myanmar (IRB number 184 (ENT)/UMM/2018), and (4) Hospital of Universiti Sains Malaysia (IRB number USM/JEPeM/19030215). Patients diagnosed with IFRS and DM at any age were identified. The diagnosis criteria of IFRS and DM were according to the ICD-10-CM codes. Patients with DM either previously diagnosed or newly diagnosed at the time of admission were included. Patients with incomplete records were excluded from the study. Diagnostic criteria for DM were a fasting plasma glucose value ≥ 7.0 mmol/L (126 mg/dl), a 2-hour post-load plasma glucose ≥ 11.1 mmol/L (200 mg/dl), a HbA1C level ≥ 6.5% (48 mmol/mol), or a random plasma glucose ≥ 11.1 mmol/L (200 mg/ dl) with the presence of signs and symptoms. (1, 154)Diagnostic criteria for IFRS were radiological imaging and/or histopathological evidence of hyphal forms within the sinus mucosa, submucosa, blood vessels, or bone.(27)

The primary outcome of this study was the overall survival. Secondary outcomes were prognostic factors for the overall survival. Duration from the admission date to either the last follow-up date or death was recorded. Variables were analyzed for prognostic factors which included: old age, high HbA1C level, ketoacidosis, white blood cell count, hyperglycemia, duration of DM, current use of diabetic medications, serum

creatinine level, the extensions of IFRS to the orbit, the cavernous sinus and intracranial cavity. Old age was defined as 60 years old.(155) High HbA1C level was defined as a level above 8.(25)Diabetic ketoacidosis was diagnosed when the patients had hyperglycemia > 250 mg/dl, a presence of either serum or urine ketone and an arterial pH < 7.3.(156) Leukopenia was defined as a white blood cell count <4,000 $x10^3$ cell per liter(157) and leukocytosis >11,000 $x10^3$ cell per liter.(158) Hyperglycemia was defined as a plasma glucose level on the admission day above 200 mg/dl.(25) Current use of diabetic medications was recorded as yes or no. A serum creatinine level greater than 1 mg/dl was defined as high. The orbital extension, the cavernous sinus extension and intracranial extension of IFRS were recorded as yes or no.

Statistical analysis

Descriptive data were presented as percentage and mean ± standard deviation. Univariate analysis was done for each variable. Significant variables were incorporated to a multivariate model. Backward stepwise Cox proportional hazard model was run to assess potential hazard ratio. Kaplan Meier curve and Log-rank test were used for analyzing survival outcomes. STATA 15 was used for the data analysis. A p-value ≤0.05 was considered statistically significant.

5.2 Results

Patients

A total of 65 diabetic patients with IFRS were identified. The mean age was 57.9±13.4 years and 60% were male. Duration of the admission date to the last follow-up date was 207±161 days. Type II diabetes accounted for 98.4% of the patients and 16 patients (24.6%) were newly diagnosed with type II diabetes at the time of admission. All previously diagnosed diabetic patients were taking medications for controlling their plasma glucose level. Seven patients (10.8%) had diabetic ketoacidosis.

Mucormycosis was diagnosed in 35.4% and aspergillosis in 35.4% of the patients. Seven patients (10.8%) had both mucormycosis and aspergillosis. One patient (1.5%) had both mucormycosis and actinomycosis. Other types of fungi such as Candida species accounted for 1.5%. The type of fungal hyphae was not specified in 6.2%. The culture results that had sterile fungal culture were reported in 6 patients (9.2%). Fifty-six patients (86.2%) had acute IFRS and 9 patients (13.8%) had chronic IFRS.

Sixty-two patients (95.4%) received antifungal treatment and three patients did not received antifungal treatment. Forty-two patients (64.6%) received amphotericin B derivatives therapy and 11 patients received amphotericin B derivatives as a sole agent. Twenty-nine patients (44.6%) received voriconazole. All patients underwent endoscopic sinus surgery. Thirty-three patients (50.8%) underwent one endoscopic sinus surgery. Seventeen patients (26.1%) and fifteen patients (23.1%) underwent two surgeries and more than two surgeries, respectively. Sinus surgery was combined with orbital surgery in 16 patients (24.6%) and neurosurgery in 3 patients (4.6%). 8(24.2%) patients out of 33 patients who received surgery for only one time died in this study . Where 2 patients out of 17 patients died in 2 times surgeries and 4 patients out of 12 patients died in 3 times surgeries.

Prognostic factors and overall survival analysis

The overall survival analysis was obtained from the data of 65 patients. The mortality rate was 21.5%. Eight out of 33 patients (24.2%) who received one endoscopic sinus surgery and six out of 32 patients (18.8%) who received multiple endoscopic sinus

surgeries died. The mean follow-up duration was 207.5±161.9 days (range 2-365 days). Thirty-one patients (47.7%) were over 60 years old. Plasma glucose levels were reported in all the 65 patients. The mean plasma glucose level was 220.1±98.7 mg/dl and 30 patients (46.2%) had plasma glucose above 200 mg/dl. HbA1C level was reported in 39 patients. The mean HbA1C level was 10.6 ±3.5 and 31 patients had HbA1C greater than 8. Duration of having diabetes was recorded in 51 patients. The mean duration of having diabetes before admission was 7.2±8.5 years. Seventeen patients (33.3%) had less than one-year duration, 17 patients (33.3%) between 1-10 years, and 17 patients (33.3%) above ten years. Sixteen patients (24.6%) did not take any diabetic medication at the time of admission. Total white blood cell count was recorded in 62 patients. The mean total white blood cell count was 14,572.3 ±24,670.3 $x10^3$ cell per liter. Two patients (3.2%) had a total white blood cell count less than 4,000 $x10^3$ cell per liter, 35 patients (56.5%) had 4,000-11,000 $x10^3$ cell per liter, and 125 patients (40.3%) had greater than 11,000 $x10^3$ cell per liter. Serum creatinine level was recorded in 63 patients. The mean serum creatinine level was 1.2±0.9 mg/dl. Thirty-five patients (55.6%) had serum creatinine level greater than 1 mg/dl. Seven patients (10.8%) had diabetic ketoacidosis. All patients had imaging records and 15 patients (23.1%) had the cavernous sinus extension, 23 patients (35.4%) had intracranial extension and 37 patients (56.9%) had the orbital extension.

Univariable logistic regression analysis revealed three statistically significant risk factors: the orbital extension (hazard ratio 4.7, 95% CI [1.1-21.2], p=0.004), the cavernous sinus extension (hazard ratio 4.7, 95% CI [1.6–13.4], p=0.004), and intracranial extension (hazard ratio 5.7, 95% CI [1.8–18.1], p=0.03). Current use of diabetic medications was a protective factor (hazard ratio 0.4, 95% CI [0.12–1.0], p=0.05). Multivariable logistic regression analysis confirmed two independent risk factors: the cavernous sinus extension (hazard ratio 5.1, 95% CI [1.4–18.2], p=0.013) and intracranial extension (hazard ratio 3.4, 95% CI [1.0-11.3], p=0.046). Current use of diabetic medications was an independent protective factor (hazard ratio 0.2, 95% CI [0.1–0.9], p=0.03). The data are displayed in Table 1. The 6-month overall survival of the patients with the cavernous sinus extension was 51.4% compared to 83.6% in the patients without the cavernous sinus extension (p <0.01). See Table 2 and Figure 1. The

6-month overall survival of the patients with intracranial extension was 53.3% compared to 88.9% in the patients without intracranial extension ($p<0.01$). See Figure 2. The 6-month overall survival of the patients who did not take any diabetic medication was 57.5% compared to 82.3% in the patients who took medications ($p=0.05$). See Figure 3.

Risk factors	Univariate analysis				Multivariate analysis			
	Hazard ratio	95% Confidence Interval		*p*-value	Hazard ratio	95% Confidence Interval		*p*-value
Orbital extension	4.7	1.1	21.2	0.042	2.7	0.6	12.4	0.204
Cavernous sinus extension	4.7	1.6	13.4	0.004	5.1	1.4	18.2	0.013
Intracranial extension	5.7	1.8	18.1	0.03	3.4	1.0	11.3	0.046
Current use of diabetic medications	0.4	0.1	1.0	0.05	0.2	0.1	0.9	0.028
Age >60	1.5	0.5	4.5	0.42				
Duration of DM >1 year	0.6	0.3	1.3	0.17				
Plasma glucose >200 mg/dl	1.5	0.5	4.4	0.44				
HbA1C >8	1.8	0.2	15.7	0.55				
Total WBC count	1.8	0.6	5.1	0.26				
Serum creatinine level >1 mg/dl	1.2	0.4	3.5	0.73				

Table 2. *Prognostic factors on overall survival of invasive fungal rhinosinusitis in diabetic patients (Retrospective)*

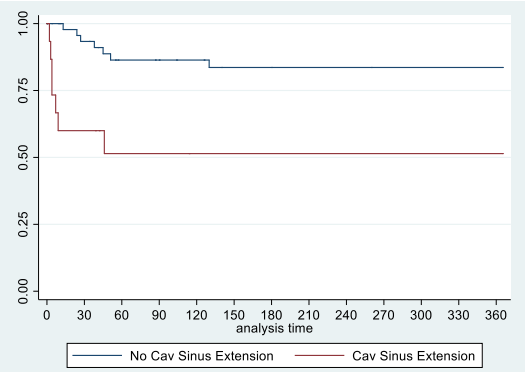
Abbreviations: DM= diabetes mellitus, WBC= white blood cell

Overall survival (%)	1 month	3 months	6 months	p-value
Intracranial extension	65.2	60.2	53.3	<0.01
No intracranial extension	97.3	88.9	88.9	
Cavernous sinus extension	60.0	51.4	51.4	<0.01
No cavernous sinus extension	93.3	86.4	83.6	
Current no use of diabetic medications	74.5	67.0	57.5	0.05
Current use of diabetic medications	89.3	82.3	82.3	

Table 3 Overall survival at 1, 3, 6 months of invasive fungal rhinosinusitis in diabetic patients who had risk factors compared to those without (Retrospective)

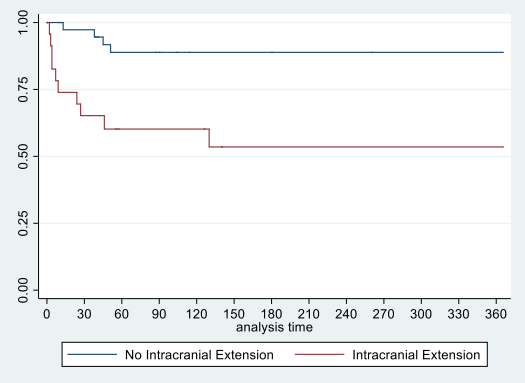
Figure 3. Kaplan Meier Estimates of overall survival for cavernous sinus extension. Significance was assessed by Log rank test. (Retrospective)

Footnote: Cav Sinus= cavernous sinus



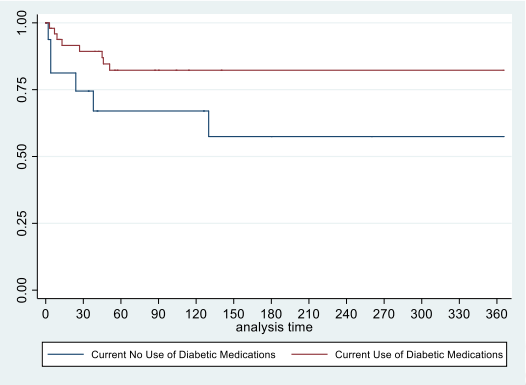
P=0.002

Figure 4. Kaplan Meier Estimates of Survival for intracranial extension. Significance was assessed by Log rank test. (Retrospective)



P= 0.001

Figure 5. Kaplan Meier Estimates of overall survival for current use of diabetic medications. Significance was assessed by Log rank test. (Retrospective)



P=0.045

5.3 Discussion

This study found that the overall survival of diabetic patients with IFRS was greatly diminished when the IFRS extension involved the cavernous sinus and intracranial cavity. Angioinvasion is a hallmark of IFRS. The resting spores of the fungi that swell and germinate within a host cause rapid filamentous growth, angioinvasion, and vessel thrombosis.(23) Tissue invasion and angioinvasion are rapid and progressive which lead to extension of the IFRS into the cavernous sinus. Common clinical manifestations of cavernous sinus involvement are spiking fevers together with bilateral orbital signs including bilateral exophthalmos, lid drop, and complete ophthalmoplegia.(153) Signs of meningeal irritation are also common in IFRS with the cavernous sinus extension. IFRS with the cavernous sinus extension is acknowledged as a fatal condition. The areas of both the cavernous sinus and intracranial extensions are high risk for endoscopic sinus and skull base debridement. As a result, total disease eradication of these areas may not be achieved. The findings of this study did not show that multiple endoscopic sinus surgeries reduced the risk.

Although the orbital extension was a significant risk factor when it was assessed by univariable logistic regression, it was no longer statistically significant by multivariable logistic regression. Therefore, the orbital extension was not an independent factor. It was significant due to its association with the cavernous sinus extension. For a total disease eradication of IFRS extension to the orbit, an orbital exenteration is suggested when significant amount of the orbital contents are invaded. Nevertheless, the orbit can be preserved in selected cases with minimal orbital involvement. In this study the authors did not acknowledge blindness from an orbital exenteration as a morbidity of IFRS because the orbital exenteration was for saving the patient's life. Besides, patients with blindness may function normally and have a good quality of life.

Current use of diabetic medications was a protective factor. The immunocompromised status of diabetic patients is related to the diabetes status. Patients with poorly controlled DM have impaired immune function. Both humoral and cellular innate immunity of the patients with diabetes are defective. Glycation end

products play a causative role in the vascular complications of DM and the decreased expression of class I major histocompatibility complex on the surface of myeloid cells. The interleukin (IL)-10 production by myeloid cells, the interferon (IFN)- γ and tumor necrosis factor (TNF)-α productions by T cells, and the secretions of IL-1and IL-6 by mononuclear cells and monocytes are inhibited.(17) The balance between complement activation and restriction is broken. As a result, poorly controlled DM activates protein kinase C which inhibits neutrophil migration, decreases the production of polymorphonuclear cells, decreases chemotaxis and decreases phagocytic activity. The mortality rate of IFRS has a wide range from 20% to 80% and depends on the diabetes status. Well-controlled DM by appropriate medications can recover the impaired immune function. However, the analysis of plasma glucose and HbA1C levels in this study did not reach statistical significance. The cut-off points of 200 mg/dl used for analyzing plasma glucose and the cut-off point of 8 for HbA1C may not be sensitive. There was missing data for HbA1C which caused non-significant results.

In line with the findings of our study, a retrospective study by Sun, et al.(159) showed that the extension of the fungal tissue invasion was a risk factor associated with the mortality rate. Data from 13 patients with IFRS from their cohort and 77 patients in the literature were assessed. Fifty-seven percent of the patients had intracranial involvement with a 74% mortality rate. This mortality rate was higher than the overall mortality rate (52%) of the patients. Likewise, a retrospective study by Jung, et al. (76) assessed 12 patients with rhinocerebral mucormycosis. The most common underlying immunocompromised diseases were DM and hematological malignancies. The overall mortality rate was 33%. All the fatal cases were DM. The mortality was related to uncontrolled underlying disease. The risk factor was the extension of disease to the orbit or intracranial cavity.(76)

This study had several limitations. First, this was a retrospective study. Medical records retrieval went back to January 2008 which was before electronic medical records were used in the hospitals. The data extraction was from a combination of electronic and hard copies. There were missing variables or incomplete data. The patients with missing variables or incomplete data were excluded from the variable

analysis. Therefore, the total number of the patients assessed for each variable was different. The small number of the patients in some variables may not have enough power to show any significance. However, the statistically significant variables showed from these small numbers were accurate and true because the authors did not make assumption on the missing data. Another limitation was the diagnostic criteria used for DM and IFRS may vary across the institutes. Nevertheless, this study followed the ICD-10-CM that have been generally accepted. Records with inappropriate diagnosis or unclear data were excluded from the study.

5.4 Conclusions

The overall mortality rate of diabetic patients with IFRS in this study was 21.5%. The extensions of IFRS to the cavernous sinus and intracranial cavity were significant risk factors which predicted death. Survival was primarily related to current use of diabetic medications. In practice, treatment should aim for controlling diabetic conditions and a restoration of the immune dysfunction to improve the patient survival.

CHAPTER 6. CONCLUSION

The overall mortality rate of diabetic patients with invasive fungal sinusitis in the systematic review was 31.8% and retrospective study was 21.5%. The extension of invasive to the cavernous sinus predicts a high mortality rate in both systematic and retrospective study. The extension of invasive fungal sinusitis to the intracranial cavity was significant risk factors which can predict the death in the data of

retrospective. Patients can have favorable overall survival when diabetic conditions are well controlled. In the retrospective study, survival was primarily related to current use of diabetic medications. In practice, treatment should aim for controlling diabetic conditions and a restoration of the immune dysfunction to improve the patient survival.

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