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Comparison of Initial Methylprednisolone dose of 1 mg/kg/day versus 2 mg/kg/day for the Treatment of Severe Acute Graft-versus-host Disease of the Lower Gastrointestinal Tract

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Abstract

Background

Severe acute lower gastrointestinal (GI) graft-versus-host disease (GVHD) is the most common cause of GVHD-related mortality in recipients after allogeneic hematopoietic cell transplantation. Although systemic glucocorticoid therapy is the standard initial therapy, the optimal dose remains unclear.

Methods

We retrospectively analyzed 57 patients with stage 2-4 (grade Ⅲ-Ⅳ) acute lower GI GVHD who received systematic glucocorticoids as initial therapy, either 1 mg/kg/day (n=31) or 2 mg/kg/day (n=26) of methylprednisolone (mPSL).

Results

Treatment responses at day 14 were comparable between the groups, with a complete response rate of 48.4% (15/31) in the 1 mg/kg group and 53.8% (14/26) in the 2 mg/kg group (p=1.00). Median cumulative prednisolone-equivalent doses by day 100 in patients initially treated with 1 and 2 mg/kg/day of mPSL were 59.6 and 88.1 mg/kg (p=0.009), respectively. There were no differences in the cumulative incidence of secondary therapy, bacteremia, fungal infection, cytomegalovirus (CMV) antigenemia, or CMV disease between the groups after mPSL treatment. However, the incidence of non-CMV viral disease (p=0.03), especially adenovirus infection (p=0.02), was significantly lower in the 1 mg/kg/day group. Overall survival, cumulative incidence of relapse or progression, and non-relapse mortality were comparable between the groups.

Conclusions

An initial mPSL dose of 1 mg/kg/day, instead of 2 mg/kg/day, might be feasible for the treatment of severe acute lower GI GVHD in terms of equivalent efficacy and reduced steroid-related toxicity.

Key Words: Acute graft-versus-host disease; Lower gastrointestinal tract; Methylprednisolone; Viral infection; Allogeneic hematopoietic cell transplantation

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Introduction

Despite recent advances in prophylactic immunosuppressive therapy, acute graft-versus-host disease (GVHD) remains a major cause of transplant-related mortality in patients receiving allogeneic hematopoietic cell transplantation (allo-HCT). The main organs affected by acute GVHD are skin, gastrointestinal (GI) tract, and liver. Severity is graded by stage in each involved organ. A large registry-based retrospective study that analyzed patients who underwent allo-HCT between 1990 and 2015 demonstrated that grade Ⅱ-Ⅳ and grade Ⅲ-Ⅳ acute GVHD occurred in 28%-40% and 11%-19% of recipients (differed depending on the time period), respectively[1]. Acute GI GVHD, which can be categorized into upper and lower GI subtypes according to clinical symptoms and pathological findings, accounts for 50%-66% of patients with acute GVHD[1]. Acute upper GI GVHD is generally indolent and controllable, whereas acute lower GI GVHD is often severe and life-threatening.

Previous studies have indicated that systemic glucocorticoid therapy with a methylprednisolone (mPSL) or prednisone (PSL)-equivalent dose of 2 mg/kg/day is considered the standard initial therapy for grade Ⅱ-Ⅳ acute GVHD during prophylaxis with immunosuppressive agents; initial mPSL dose higher than 2 mg/kg/day showed no beneficial effect on survival outcomes after steroid therapy[2,3]. Meanwhile, recent studies have demonstrated that a lower initial PSL dose (0.5-1.0 mg/kg/day) has no adverse impact on acute GVHD control and survival[4,5]. However, these studies lack detailed data regarding therapeutic response by initial steroid dose and involved a variety of organs. Notably, susceptibility to steroid therapy could differ by target organ[5]. We therefore conducted a retrospective study to evaluate the effect of initial steroid dose on newly diagnosed severe acute lower GI GVHD, which is the greatest cause of GVHD-related mortality in patients undergoing allo-HCT[6,7].

Methods

Data collection and patient selection

All patients aged 18 years or older who underwent allo-HCT at Osaka Metropolitan University Hospital between July 2013 and June 2020 and received systemic glucocorticoid therapy with a mPSL dose of 1 or 2 mg/kg/day as initial treatment for stage 2-4 (grade Ⅲ-Ⅳ) acute lower GI GVHD were included. Patients who received oral beclomethasone dipropionate as topical therapy were excluded. The study protocol was approved by the ethics committee of the Graduate School of Medicine, Osaka Metropolitan University in accordance with the Declaration of Helsinki (approval number: 2022).

Treatment for acute lower gastrointestinal GVHD

Patients who presented with stage 2-4 acute lower GI GVHD received systematic glucocorticoid with 1 or 2 mg/kg of mPSL in two divided doses per day. The initial mPSL dose was determined at the discretion of the attending physician. If the patient achieved complete remission (CR)[8], tapering of the glucocorticoid dose (−10% per 5-7 days) began 6-14 days after the initiation of treatment. The immunosuppressant agent used for GVHD prophylaxis was continued during the steroid treatment. For patients with steroid-refractory acute GVHD, defined as clear progression after 3-5 days or no response after 5-7 days of mPSL treatment[9], secondary therapy was initiated with dose escalation of mPSL from 1 to 2 mg/kg per day (only in patients initially treated with mPSL at 1 mg/kg/day), mPSL pulse, intra-arterial steroid infusion (IA-steroid)[10], anti-thymocyte globulin (ATG), or mesenchymal stem cells (MSCs). Decision regarding the timing and selection of secondary therapy was made at the discretion of the physician in charge.

Supportive care and monitoring for infectious diseases

In principle, all patients received levofloxacin 500 mg/day as a prophylactic antibiotic until neutrophil engraftment or until a switch to another antibiotic. Fluconazole 200 mg/day was also administered until day 100 as standard antifungal prophylaxis. Fluconazole was switched to an antimold agent (voriconazole or itraconazole) at the initiation of systemic steroid therapy. In addition, patients received 600 mg/day of acyclovir as prophylaxis for herpes simplex virus (HSV) and varicella-zoster virus (VZV) until neutrophil engraftment; the dose was subsequently reduced to 200 mg/day and continued until the discontinuation of all immunosuppressants or at least 1 year after allo-HCT. Trimethoprim-sulfamethoxazole was given as prophylaxis against *Pneumocystis jirovecii* except for the period from day −1 to neutrophil engraftment.

Screening for fungal disease was performed with weekly examination of serum β-D-glucan and galactomannan levels as well as portable chest X-rays. Cytomegalovirus (CMV) antigenemia was monitored with weekly C7HRP. Preemptive treatment with ganciclovir or foscarnet was initiated for patients with confirmed CMV antigenemia[11].

Study endpoints and definitions

The primary endpoint was the treatment response to initial mPSL therapy at day 14. The secondary endpoints included treatment responses at days 3, 5, and 7; the cumulative incidence of secondary therapy, bacteremia, invasive fungal infection, viral infection, relapse or progression (Rel/Prog), and non-relapse mortality (NRM); and overall survival (OS) after mPSL treatment. The cumulative PSL-equivalent glucocorticoid dose was calculated as the total amount administered by days 30, 60, 90, and 100 after the start of mPSL therapy.

The diagnosis and grading of acute GVHD and response assessment were performed according to traditional criteria[8,12]. Severe acute lower GI GVHD was defined as a digestive tract disorder that presented with diarrhea exceeding 1000 mL per day (stage 2-4) after engraftment when other GVHD-like conditions could be excluded[8,12]. Bacteremia was defined as an infectious condition with detection of the causative bacteria through blood culture testing. Fungal infection was defined as probable or proven disease according to guideline from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium[13]. CMV antigenemia was defined as at least 2 pp65 antigen-positive cells per 50000 while blood cells based on the C7HRP method. CMV infection was defined as previously described[14]. Other viral infection was defined as symptomatic disease with evidence of viral etiology, including adenovirus (ADV), BK virus (BKV), HSV, human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and VZV. Rel/Prog was defined as any initial detection of hematological, radiographic, or pathological evidence of primary disease. NRM was defined as death without Rel/Prog. OS was defined as the time from the date of allo-HCT to death or last follow-up. Conditioning intensity (myeloablative conditioning [MAC] vs reduced intensity conditioning [RIC])[15,16], Karnofsky performance status (KPS)[17], and hematopoietic cell transplantation-comorbidity index (HCT-CI)[18], were evaluated according to previously established criteria. With respect to disease status at the time of allo-HCT, acute leukemia and malignant lymphoma in the first or second CR, chronic myeloid leukemia in the first or second chronic phase, myelodysplastic syndrome with refractory anemia with or without ringed sideroblasts, and benign hematological disorders were defined as being standard risk, while other malignant diseases were defined as being high risk[19].

Statistical analysis

Baseline characteristics and treatment outcomes of severe acute lower GI GVHD between the 1

and 2 mg/kg/day groups were compared using Fisher's exact test for categorical variables and the Wilcoxon's rank-sum test for continuous variables. OS was estimated using the Kaplan-Meier method. The log-rank test was used to compare the outcome between the two groups. The cumulative incidence of secondary therapy, individual infection, Rel/Prog, and NRM was estimated using Gray's method with death considered to be a competing risk for secondary therapy or infectious event, death without Rel/Prog as a competing risk for Rel/Prog, and Rel/Prog as a competing risk for NRM.

Two-sided p-values of <0.05 were considered statistically significant. All statistical analyses were performed with EZR version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)[20].

Results

Patient characteristics

During the study period, 309 patients received allo-HCT at our department, of which 109 recipients (35.3%) developed acute GVHD of the GI tract. Among them, 31 patients who received systemic mPSL at a dose of 1 mg/kg/day, and 26 patients who received systemic mPSL at a dose of 2 mg/kg/day as an initial treatment for severe acute lower GI GVHD met the eligibility criteria (Fig. 1). Demographic and transplant characteristics are presented in Table 1. There were no significant differences between the groups in terms of age, sex, disease type, KPS, disease risk, conditioning intensity, HCT-CI, total body irradiation use, donor type, GVHD prophylaxis, ATG use, post-transplantation cyclophosphamide use, CMV serostatus, number of allo-HCTs, duration from allo-HCT to mPSL therapy, acute lower GI GVHD stage, and involved non-GI organs. None of the patients in either group had grade Ⅳ acute GVHD.

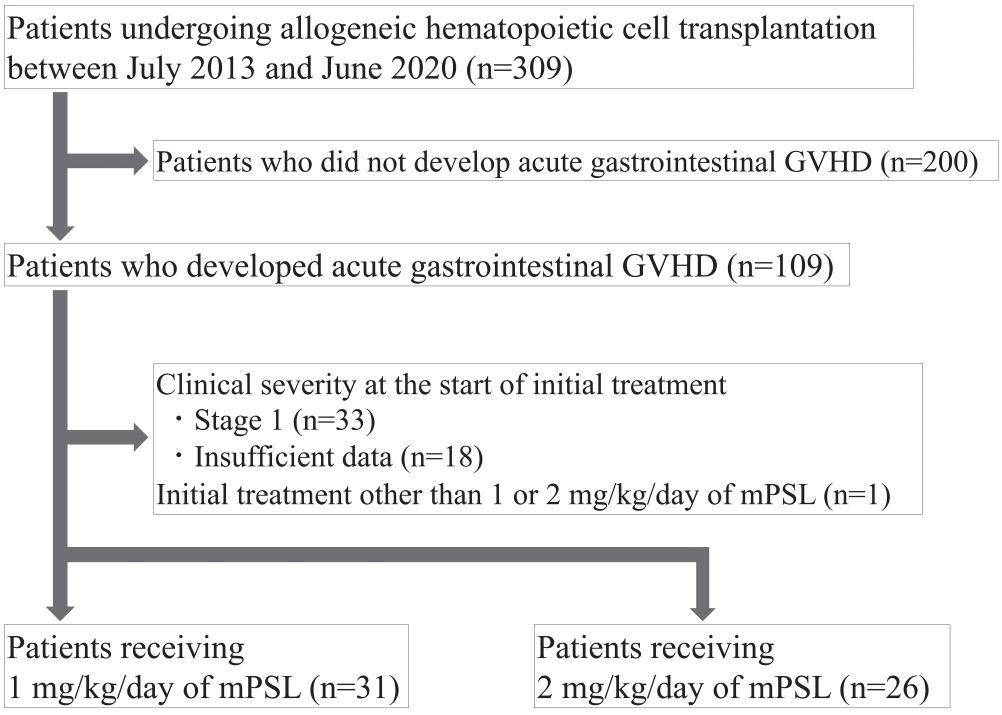

Figure 1. Flowchart of patient selection. GVHD, graft-versus-host disease; and mPSL, methylprednisolone.

Table 1. Characteristics of the study patients

Initial mPSL dose Number of patients	1 mg/kg/day n=31	2 mg/kg/day n=26	p-value
Patient age, years (median, IQR)	43 (38-54)	51 (43-58)	0.11
Sex (%)			
Male	19 (61.3)	16 (61.5)	1.00
Female	12 (38.7)	10 (38.5)	
Disease (%)			
AML	11 (35.5)	7 (26.9)	0.52
ALL/LBL	6 (19.4)	5 (19.2)	
MDS	5 (16.1)	7 (26.9)	
ML	5 (16.1)	4 (15.4)	
AA	4 (12.9)	1 (3.8)	
Other	0 (0.0)	2 (7.7)	
KPS (%)			
＞ 80	25 (80.6)	19 (73.1)	0.54
≦ 80	6 (19.4)	7 (26.9)	
Disease risk (%)			
Standard	13 (41.9)	10 (38.5)	1.00
Advanced	18 (58.1)	16 (61.5)	
Conditioning intensity (%)			
MAC	12 (38.7)	10 (38.5)	1.00
RIC	19 (61.3)	16 (61.5)	
HCT-CI (%)			
Low	13 (41.9)	10 (38.5)	1.00
Intermediate	11 (35.5)	10 (38.5)	
High	7 (22.6)	6 (23.1)	
TBI use (%)	11 (35.5)	9 (34.6)	1.00
Donor type (%)			
Matched related PB	2 (6.5)	3 (11.5)	0.79
Matched unrelated BM	4 (12.9)	1 (3.8)	
Mismatched unrelated BM	2 (6.5)	1 (3.8)	
Haploidentical related PB	14 (45.2)	13 (50.0)	
Unrelated cord blood	9 (29.0)	8 (30.8)	
GVHD prophylaxis (%)			
CyA based	6 (19.4)	5 (19.2)	1.00
Tac based	25 (80.6)	21 (80.8)	
ATG use (%)	0 (0.0)	1 (3.8)	0.46
PTCy use (%)	14 (45.2)	15 (57.7)	0.43
CMV serostatus (%)			
Recipient^{+}/Donor^{+}	11 (35.5)	12 (46.2)	0.06
Recipient^{+}/Donor^{-}	13 (41.9)	14 (53.8)	
Recipient^{-}/Donor^{+}	1 (3.2)	0 (0.0)	
Recipient^{-}/Donor^{-}	6 (19.4)	0 (0.0)	
Number of allo-HCTs (%)			
1	24 (77.4)	21 (80.8)	1.00
2	5 (16.1)	4 (15.4)	
3	2 (6.5)	1 (3.8)	
Days from allo-HCT to mPSL treatment (median, IQR)	14 (9-20)	15 (8-26)	0.87
Stage of acute lower GI GVHD at time of mPSL treatment (%)			
2	18 (58.1)	14 (53.8)	0.68
3	13 (41.9)	11 (42.3)	
4	0 (0.0)	1 (3.8)	
Involved organ at time of mPSL treatment (%)			
Lower GI	24 (77.4)	22 (84.6)	0.86
Lower GI + skin	6 (19.4)	4 (15.4)	
Lower GI + liver	1 (3.2)	0 (0.0)	
Grade of acute GVHD at mPSL treatment (%)			
Ⅲ	31 (100.0)	26 (100.0)	NE
Ⅳ	0 (0.0)	0 (0.0)	

AA, aplastic anemia; allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; ALL/LBL, acute lymphoblastic leukemia/lymphoblastic lymphoma; ATG, anti-thymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CyA, cyclosporin A; GI, gastrointestinal; GVHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation-comorbidity index; IQR, interquartile range; KPS, Karnofsky performance scale; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; ML, malignant lymphoma; mPSL, methylprednisolone; NE, not estimable; PB, peripheral blood; PTCy, post-transplant cyclophosphamide; RIC, reduced intensity conditioning; Tac, tacrolimus; and TBI, total body irradiation.

Table 2. Treatment outcomes

Initial mPSL dose	1 mg/kg/day (n=31)	2 mg/kg/day (n=26)	p-value
Diarrhea volume, mL (Median, IQR)			
Day 1	1395 (1293-1961)	1448 (1254-2094)	0.65
Day 3	870 (463-1407)	1328 (508-1751)	0.29
Day 5	450 (235-665)	698 (90-1471)	0.31
Day 7	350 (128-693)	115 (0-995)	0.47
Day 14	25 (0-408)	0 (0-165)	0.16
Response (%)			
Day 3			
Complete response	7 (22.6)	5 (19.2)	0.24
Partial response	14 (45.2)	7 (26.9)	
Mixed response	2 (6.5)	0 (0.0)	
No change	6 (19.4)	9 (34.6)	
Progression	2 (6.5)	3 (11.5)	
Secondary therapy	0 (0.0)	2 (7.7)	
Day 5			
Complete response	10 (32.3)	10 (38.5)	0.02
Partial response	16 (51.6)	6 (23.1)	
Mixed response	2 (6.5)	0 (0.0)	
No change	1 (3.2)	4 (15.4)	
Progression	1 (3.2)	0 (0.0)	
Secondary therapy	1 (3.2)	6 (23.1)	
Day 7			
Complete response	16 (51.6)	13 (50.0)	0.17
Partial response	8 (25.8)	3 (11.5)	
Mixed response	2 (6.5)	0 (0.0)	
No change	1 (3.2)	1 (3.8)	
Progression	0 (0.0)	0 (0.0)	
Secondary therapy	4 (12.9)	9 (34.6)	
Day 14			
Complete response	15 (48.4)	14 (53.8)	1.00
Partial response	1 (3.2)	0 (0.0)	
Mixed response	2 (6.5)	1 (3.8)	
No change	0 (0.0)	0 (0.0)	
Progression	1 (3.2)	0 (0.0)	
Secondary therapy	12 (38.7)	11 (42.3)	
Secondary therapy (%)			
Yes	17 (54.8)	14 (53.8)	1.00
No	14 (45.2)	12 (46.2)	
Type of secondary therapy (%)			
mPSL 1 mg → 2 mg	11 (64.7)	–	<0.001
mPSL pulse	3 (17.6)	7 (50.0)	
Intra-arterial steroid infusion	3 (17.6)	2 (14.3)	
Anti-thymocyte globulin	0 (0.0)	1 (7.1)	
Mesenchymal stem cells	0 (0.0)	4 (28.6)	
Secondary therapy other than mPSL dose escalation (%)			
Yes	14 (45.2)	10 (38.5)	0.79
No	17 (54.8)	16 (61.5)	
Type of secondary therapy other than mPSL dose escalation (%)			
Intra-arterial steroid infusion	13 (92.9)	2 (20.0)	<0.001
Anti-thymocyte globulin	0 (0.0)	1 (10.0)	
Mesenchymal stem cells	1 (7.1)	7 (70.0)	

IQR, interquartile range; and mPSL, methylprednisolone.

Treatment response

The treatment responses of the 1 and 2 mg/kg/day groups are described in Table 2. There were no significant differences between the two groups except for response at day 5 (p=0.02). A total of 16 patients (51.6%) in the 1 mg/kg/day group and 14 (53.8%) in the 2 mg/kg/day group had a CR or partial response at day 14 after mPSL therapy. CR was achieved in 15 patients (48.4%) of the 1 mg/kg/day group and 14 (53.8%) of the 2 mg/kg/day group.

Cumulative glucocorticoid dose

Median cumulative PSL-equivalent doses by days 30, 60, 90, and 100 in patients treated initially with 1 or 2 mg/kg/day of mPSL were 32.6 vs 57.9 (43.7% lower in the 1 mg/kg/day group; p<0.001), 48.5 vs 79.9 (39.3% lower; p=0.001), 57.0 vs 87.1 (34.6% lower; p=0.002), and 59.6 vs 88.1 mg/kg (32.3% lower; p=0.009), respectively (Fig. 2).

Secondary therapy

The cumulative incidence of secondary therapy at day 100 after initiation of mPSL therapy was 54.8% in the 1 mg/kg/day group and 53.8% in the 2 mg/kg/day groups (p=0.72) (Fig. 3A). During the entire follow-up period, 17 patients in the 1 mg/kg/day group and 14 patients in the 2 mg/kg/day group required secondary immunosuppressive therapy. The most common type of secondary therapy in the 1 mg/kg/day group was mPSL dose escalation (1 to 2 mg/kg/day) (n=11; 64.7%), followed by mPSL pulse (n=3; 17.6%) and IA-steroid (n=3; 17.6%) among the 17 patients. Among the 14 patients in the 2 mg/kg/day group, the secondary therapies included mPSL pulse (n=7; 50.0%), followed by MSCs (n=4; 28.6%) and IA-steroid (n=2; 14.3%). The cumulative incidence of secondary therapy excluding glucocorticoid dose escalation at day 100 after mPSL therapy in the 1 mg/kg/day and 2 mg/kg/day group was 45.2% and 38.5%, respectively (p=0.98) (Fig. 3B). A total of 14 patients in the 1 mg/kg/day group and 10 in the 2 mg/kg/day group received secondary therapy other than a higher dose of mPSL throughout the observation period. The most common type of secondary therapy in the 1 mg/kg/day group was IA-steroid (n=13; 92.9%) followed by MSCs (n=1; 7.1%) among the 14 patients, whereas, in the 2 mg/kg/day group, the most common type of secondary therapy was MSCs (n=7; 70.0%), followed by IA-steroid (n=2; 20.0%) and ATG (n=1; 10.0%) among the 10 patients (Table 2).

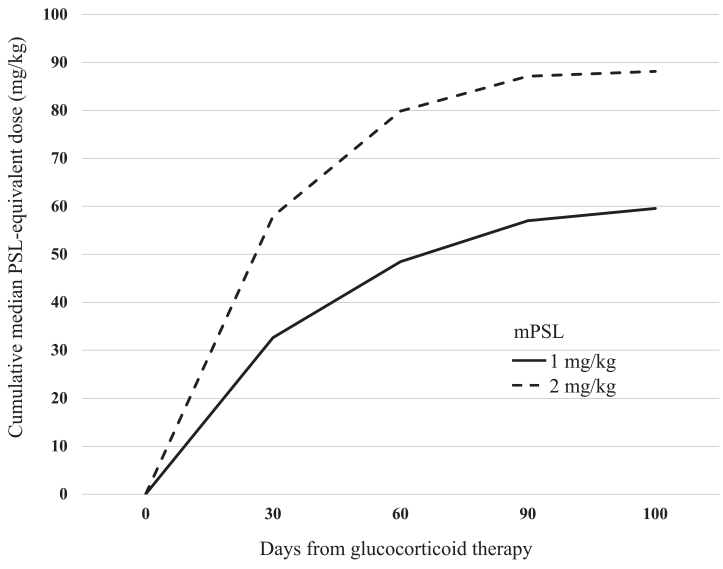

Figure 2. Cumulative median prednisone (PSL)-equivalent steroid use by initial methylprednisolone (mPSL) dose.

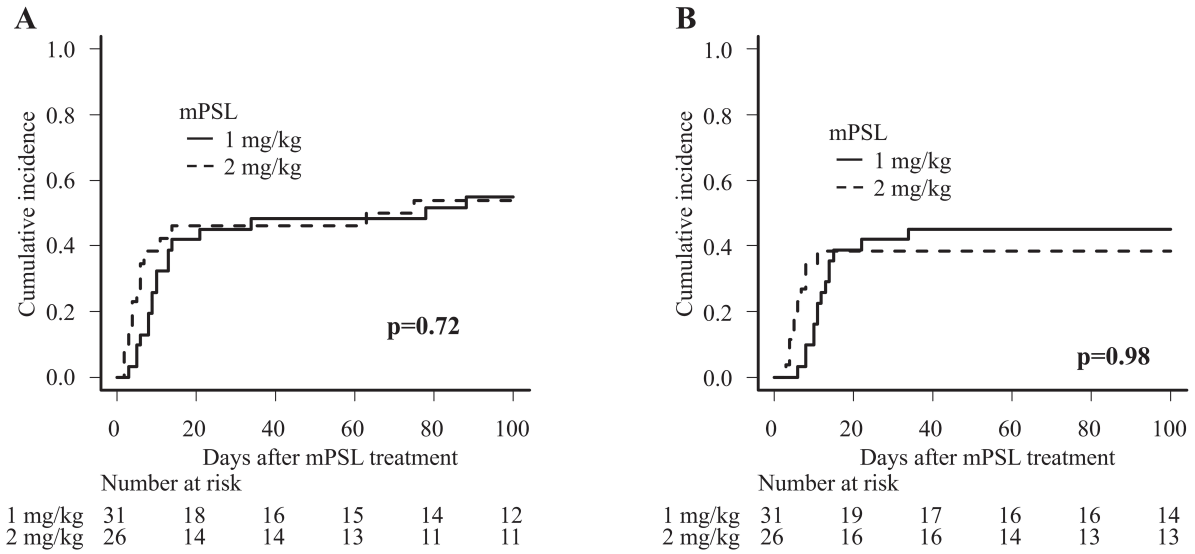

Figure 3. A) Cumulative incidence of secondary therapy including methylprednisolone (mPSL) dose escalation or **B)** excluding mPSL dose escalation by initial mPSL dose.

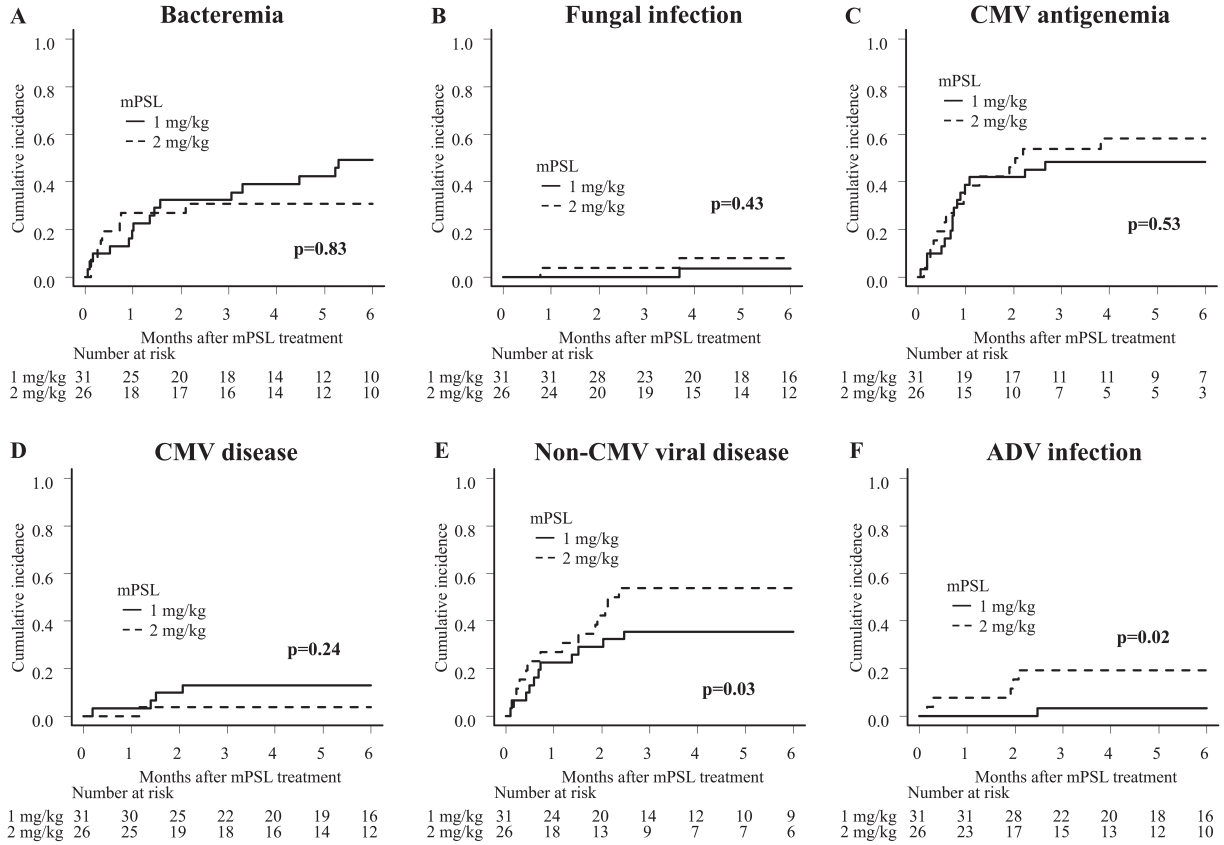

Figure 4. Cumulative incidence of individual infections by initial methylprednisolone (mPSL) dose. ADV, adenovirus; and CMV, cytomegalovirus.

Infectious events

The cumulative incidences of bacteremia, fungal infection, CMV antigenemia, CMV disease, viral diseases other than CMV (ADV, BKV, HSV, HHV-6, EBV, or VZV) at 6 months after 1 or 2 mg/kg/day

Table 3. Causative pathogens

Initial mPSL dose Number of patients	1 mg/kg/day n=31	2 mg/kg/day n=26
Bacteremia (%)		
Corynebacterium species	2 (6.5)	0 (0.0)
Enterobacter cloacae	1 (3.2)	0 (0.0)
Enterococcus faecium	4 (12.9)	2 (7.7)
Escherichia coli	1 (3.2)	0 (0.0)
Pseudomonas aeruginosa	0 (0.0)	1 (3.8)
Staphylococcus aureus	1 (3.2)	1 (3.8)
Staphylococcus epidermidis	7 (22.6)	5 (19.2)
Staphylococcus haemolyticus	1 (3.2)	3 (11.5)
Staphylococcus hominis	1 (3.2)	0 (0.0)
Stenotrophomonas maltophilia	0 (0.0)	1 (3.8)
Fungal infection (%)		
Aspergillus species	2 (6.5)	1 (3.8)
Candida species	0 (0.0)	1 (3.8)
Pneumocystis jirovecii	0 (0.0)	1 (3.8)
Viral infection (%)		
Adenovirus	1 (3.2)	6 (23.1)
BK virus	6 (19.4)	8 (30.8)
Cytomegalovirus antigenemia	15 (48.4)	15 (57.7)
Cytomegalovirus disease	4 (12.9)	1 (3.8)
Epstein-Barr virus	2 (6.5)	4 (15.4)
Human herpesvirus 6	2 (6.5)	4 (15.4)
Herpes simplex virus	1 (3.2)	0 (0.0)
Varicella-zoster virus	1 (3.2)	3 (11.5)

mPSL, methylprednisolone.

of mPSL were 49.2% vs 30.8% (p=0.83), 3.4% vs 7.9% (p=0.43), 48.4% vs 58.3% (p=0.53), 12.9% vs 3.8% (p=0.24), and 35.5% vs 53.8% (p=0.03), respectively (Figs. 4A-E). Detailed information on the causative pathogens is described in Table 3. The most prevalent organism causing bacteremia was *Staphylococcus epidermidis* in both groups. Among five patients who developed fungal disease, three patients developed probable invasive pulmonary aspergillosis (two in the 1 mg/kg/day group and one in the 2 mg/kg/day group), one developed candidemia (2 mg/kg/day group), and one developed *Pneumocystis jirovecii* pneumonia (2 mg/kg/day group). A majority of non-CMV viral infections were caused by ADV or BKV, all of which developed as hemorrhagic cystitis. Among the non-CMV infections, only ADV infection was significantly less common in the 1 mg/kg/day mPSL group compared with the 2 mg/kg/day group, with a cumulative incidence of 3.2% and 19.2% at 6 months after mPSL treatment (p=0.02) (Fig. 4F).

OS, Relapse/Progression, NRM

With a median observation period of 694 days after mPSL treatment for surviving patients in the cohort, 2-year OS in the 1 and 2 mg/kg/day groups was 36.8% and 35.8%, respectively (p=0.79) (Fig. 5A). The cumulative incidence of Rel/Prog and NRM at 2 years was 46.5% vs 21.2% (p=0.08) (Fig. 5B) and 26.3% vs 40.0% (p=0.13) (Fig. 5C), respectively.

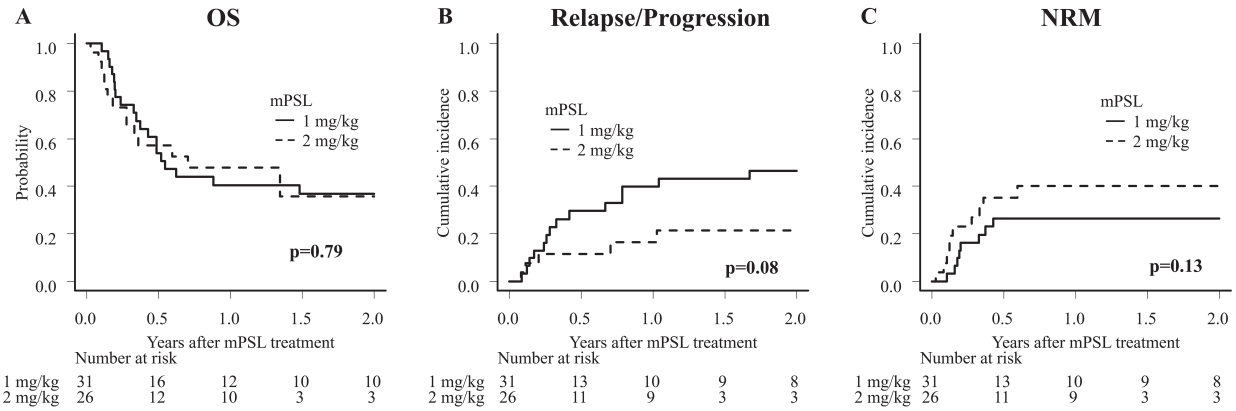

Figure 5. A) Overall survival, **B)** cumulative incidence of relapse or progression, and **C)** non-relapse mortality by initial methylprednisolone (mPSL) dose. NRM, non-relapse mortality; and OS, overall survival.

Discussion

This retrospective study revealed that an initial mPSL dose of 1 mg/kg/day has comparable therapeutic efficacy to 2 mg/kg/day at day 14 in allograft recipients affected by severe acute lower GI GVHD. Although the treatment response at day 5 was more favorable in the 1 mg/kg/day group, we were unable to definitively conclude that the initial mPSL dose of 1 mg/kg/day was superior to that of 2 mg/kg/day because of a potential selection bias. However, it suggests that there could be a subset of patients in which acute lower GI GVHD can be adequately controlled with an initial mPSL dose of 1 mg/kg/day, even in cases with a severe presentation. The cumulative steroid dose in PSL equivalents was approximately 30%-40% lower in the 1 mg/kg/day group compared to the 2 mg/kg/day group. The incidence of bacteremia, fungal infection, and CMV infection did not differ between the two groups, but the incidence of non-CMV infection, particularly ADV infection, was significantly lower in the 1 mg/kg/day group. Nonetheless, the dose difference did not affect the incidence of Rel/Prog, NRM, or OS following mPSL treatment.

Our results were consistent with those from previous studies that showed a glucocorticoid dose below the standard of care did not weaken the therapeutic effect and adversely affect survival after treatment of acute GVHD with involvement of various organs. Mielcarek et al reported that patients given an initial PSL dose of 1 mg/kg/day had approximately a 50% lower cumulative glucocorticoid dose by day 100 compared to those receiving a dose of 2 mg/kg/day[4]. They also found a nearly 50% decrease in the incidence of invasive fungal infection, but comparable rates of relapse, NRM, and OS. However, patients presented with grade Ⅲ or higher acute GVHD accounted for only 9.7% of the entire cohort, which limited the conclusions of the study to those with grade Ⅰ-Ⅱ acute GVHD. Thus, they subsequently conducted a prospective, randomized controlled trial to compare the initial dose of PSL in two cohorts: grade Ⅱa (upper GI symptoms, stool volume <1.0 L/day, rash involving <50% of body surface, no hepatic dysfunction) and grade Ⅱb or higher (rash involving ≧50% of body surface, stool volume ≧1.0 L/day, or hepatic involvement). The comparison involved PSL doses of 0.5 vs 1 mg/kg and 1 vs 2 mg/kg per day in the grade Ⅱa and grade Ⅱb-Ⅳ groups, respectively. That study showed that lower initial PSL dose was safe and effective in both cohorts in terms of comparable relapse incidence, NRM, OS, and steroid-related toxicity (infection, hyperglycemia, hypertension, myopathy, and quality of life)[5]. However, contrary to our results, that study revealed no differences

in the incidence of viral infection between steroid dose groups. This is probably because that study included only CMV reactivation, CMV disease, and viral lower respiratory tract infection as viral infection[5].

These previous studies have also reported that patients treated initially with lower steroid doses are more likely to require second-line therapy with non-glucocorticoid agents[4,5]. However, in our study, we found no differences in the incidence of secondary therapy between the groups. The discrepancy could be due to differences in race or ethnicity of donors and recipients across studies. It has been shown that Japanese patients have a lower risk of severe acute GVHD than Caucasians and individuals of other races[21-23]. The relative homogeneity of minor histocompatibility antigens in the Japanese population might have enabled a lower initial dose of mPSL to control severe acute GVHD without additional immunosuppressive therapy.

Although the initial steroid dose is crucial in terms of therapeutic effectiveness, cumulative steroid dose may be of greater importance in the context of adverse events, particularly infectious complications. Several studies have shown an association between the cumulative steroid dose and infectious events in allo-HCT recipients. Matsumura-Kimoto et al demonstrated that cumulative PSL-equivalent glucocorticoid dose ≧55 mg/kg during the first 4 weeks contributed to a higher incidence of fungal infection and dose ≧23 mg/kg was correlated with an increased risk of non-CMV disease in recipients after treatment of severe acute GVHD[24]. Most patients in the study continued with fluconazole as antifungal prophylaxis after the initiation of glucocorticoid therapy, whereas the majority of our patients received voriconazole or itraconazole after mPSL treatment. This difference could explain the discrepancy between the study by Matsumura-Kimoto et al and ours in the association between steroid dose and invasive fungal infection. Furthermore, Matsumura-Kimoto et al revealed that most non-CMV infections were cystitis caused by ADV or BKV, which was in line with our results. On the other hand, Watanabe et al reported that high-dose steroids (PSL-equivalent dose ＞7 mg/kg) was associated with an increased risk of bacteremia and CMV antigenemia[25]. The difference in causative pathogens related to steroid use between the study and ours could be due to differences in study populations and analytical methods. The study by Watanabe et al included only 8.8% of patients with grade Ⅲ or higher acute GVHD and examined the risk of infection in patients who received low- or high-dose steroid therapy compared with those not receiving steroids[25]. These conditions significantly differed from those of our study.

The present study has several limitations inherent to its single-center, retrospective nature. First, the study population was small. Patients were heterogeneous in terms of transplant characteristics such as underlying hematological disorder, disease risk, donor source, and GVHD prophylaxis. Second, we were unable to completely eliminate selection bias in the decision to use either 1 or 2 mg/kg/day of mPSL since the choice largely depended on the attending physician. The rapidity of GI symptom progression was also important in the dose selection, but it could not be taken into consideration in the present analysis. Despite these limitations, in contrast to prior studies, our study focused exclusively on severe acute lower GI GVHD and conducted a detailed comparative analysis according to the initial mPSL dose. The background characteristics of the two dose groups were comparable. Besides, patients using oral beclomethasone dipropionate, which could potentially affect the therapeutic effect of mPSL, were rigorously excluded. Our results could provide physicians with valuable information to facilitate the selection of mPSL dose in allo-HCT recipients with severe acute lower GI GVHD.

In conclusion, therapeutic response to an initial mPSL dose of 1 mg/kg/day was feasible and not inferior to that of 2 mg/kg/day in patients with severe acute lower GI GVHD. The spared glucocorticoid exposure in the 1 mg/kg/day group led to a lower incidence of non-CMV infection, particularly ADV infection, and did not compromise survival outcomes after mPSL treatment. These results showed the potential to select 1 mg/kg/day of mPSL to treat this severe form of acute GVHD.

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Interstitial Microwave Heat Generation Enhanced by Topical Glycerol Infusion

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Abstract

Background

Conversion of microwave energy to heat in tissue reduces significantly during microwave ablation. We investigated whether the topical infusion of glycerol during interstitial microwave irradiation augmented the conversion.

Materials and Methods

Glycerol, a dielectric liquid at room temperature with boiling point of approximately 290℃, was continuously infused at 0.1mL/min into the space between a microwave electrode and fresh myoma tissue using a syringe pump during microwave irradiation at 2.45 GHz, 70 W for 1200 s. Saline was used instead of glycerol in the control experiment. Tissue temperatures at 20 mm and 30 mm from the electrode were monitored during microwave irradiation.

Results

Temperature elevation with glycerol infusion was 39.7℃, less than that with saline infusion at 1200 s at 20 mm from electrode. However, temperature elevation was 19.8℃ with glycerol infusion, whereas it was only 5.2℃ with saline infusion at 1200 s at 30 mm.

Conclusions

Glycerol topically infused around a microwave electrode tip retains heat generation near the irradiation site and provides an augmented heat supply to the myoma tissue at 30 mm from the microwave electrode.

Key Words: Microwave ablation; Glycerol; Topical infusion; Relative dielectric loss factor; Interstitial microwave irradiation

Introduction

In microwave ablation (MWA), water molecules and electrolytes, such as Na^+ and Cl^-, in the tissue are responsible for microwave heat generation, where former plays the main role. Tissue temperature in the vicinity of a microwave electrode easily exceeds 100℃, the boiling point of water, during MWA. Hence, water loss from the tissue occurs, followed by tissue charring near the microwave electrode.

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Conversion of microwave energy to heat in tissue reduces significantly at temperatures exceeding 100℃. Although microwave heating by the remaining electrolytes continues at temperatures exceeding 100℃, the initial efficiency of heat generation is lost[1].

Additionally, the heat generated by a dielectric substance during microwave irradiation changes proportionately with the relative dielectric loss factor (RDLF). Because the RDLF of water decreases as temperature elevates up to 100℃[2], the physical characteristics of water result in it being not always suitable for MWA. Therefore, transcervical microwave myolysis (TCMM) cannot be used to treat tumors >70 mm in diameter[3].

When dielectric liquid with a boiling point higher than 100℃, which can be safely utilized in living tissue is infused around the microwave electrode tip, efficient heat generation could continue to temperatures exceeding 100℃. Glycerol is a dielectric liquid with a boiling point of 290℃ and is a clinically safe substance[4]. We examined whether topical glycerol infusion during interstitial microwave irradiation augmented heat supply in myoma tissue at 30 mm from a microwave electrode.

Methods

Fresh surgical specimens of uterine myomas (>60 mm in diameter) were prepared for interstitial microwave irradiation. Preoperative diagnostic imaging using ultrasonography and magnetic resonance imaging revealed that every specimen had the characteristics of a typical myoma, which agreed with the pathological diagnosis obtained later.

A microwave tissue coagulator (Microtaze AZM-520, Alfresa Pharma, Osaka, Japan) supplying microwaves at 2.45 GHz through a coaxial cable to a microwave electrode (1.6 mm diameter) was used. Tissue temperature was monitored using a fiber-optic thermometer (ReFlex, Nortech Fibronic

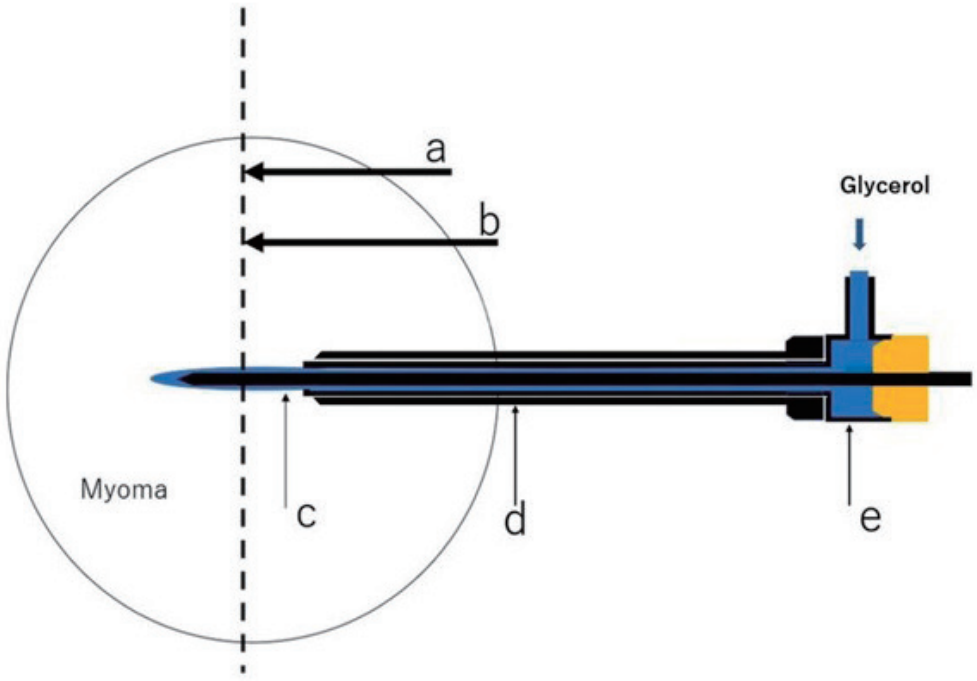

Figure 1. Schema of the infusion system.
a: sensor at 20 mm. b: sensor at 30 mm. c: microwave electrode 1.6 mm in diameter. d: needle sheath. e: customized infusion tube with a rubber stopper.

Inc., Quebec, Canada), and a syringe pump was used to infuse glycerol or saline.

Figure 1 shows a schematic of the microwave irradiation with glycerol infusion and temperature monitoring. A small amount of 97% glycerol (FUJIFILM Wako Pure Chemical Co. Osaka, Japan) was infused continuously at 0.1 mL/min with a syringe pump. To evaluate the temperature gradient in the tissue, the tissue temperature was monitored during microwave irradiation using a fiber-optic thermometer. The thermometer sensors were set at 20 mm and 30 mm from the surface of the microwave electrode tip. A guiding needle was inserted up to the center of the myoma under ultrasonic guidance and the inner needle was removed. After the sheath was filled with glycerol using a syringe pump in the manual mode, a microwave electrode covered with a customized infusion tube was inserted in the sheath. The tumor was exposed to microwave radiation at 70 W using a panel setting for 1200 s. When the generator power was set to 70 W, the output at the microwave electrode tip was 21 W at room temperature[5].

Results

Temperature elevation rate (TER) was defined as the average change in the rate of the tissue temperature-time curve. When saline was infused instead of glycerol at 70 W, the TER between 600 s and 1200 s at 20 mm decreased from 0.036 to 0.020℃/s, while that at 30 mm from a microwave electrode remained almost constant at 0.008℃/s, as derived from temperature-time curve. Tissue temperature at 1200 s of irradiation rose by 49.1℃ at 20 mm and by 5.2℃ at 30 mm. The tissue temperature with saline infusion at 20 mm from the microwave electrode showed a small short fall at 900 seconds unexpectedly, although that did not affect the temperature-time curve for 30 mm with saline infusion.

Microwave irradiation with a continuous infusion of glycerol elevated the tissue temperature for 1200s. TER between 600 s and 1200 s at 20 mm and 30 mm from the microwave electrode were 0.045 and 0.025℃/s, respectively. The TER remained almost constant from 200 to 1200 s at 20 and 30 mm. At 20 and 30 mm, the TER was low during the first 200 s of microwave irradiation. Tissue temperature at 1200 s of irradiation rose 39.7℃ and 19.8℃ at 20 mm and 30 mm, respectively (Fig. 2). The myoma tissue near the microwave electrode shrank without forming a black charring. A

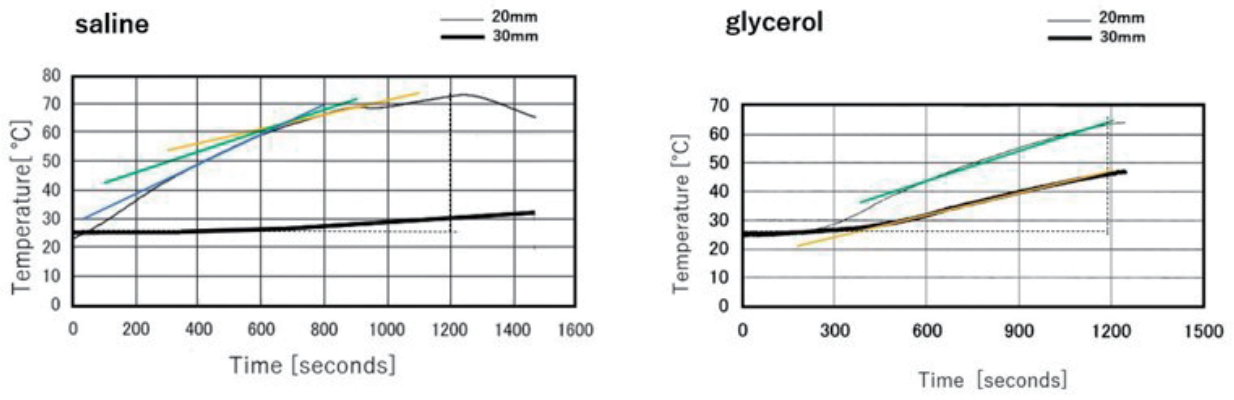

Figure 2. Change in tissue temperature.
Left: with saline infusion. Right: with glycerol infusion.
The blue, green, and yellow lines represent the slope and linearity of the curves between 600 and 1200 s. The blue, green, and yellow lines indicate the TER at 0.075, 0.045, and 0.025℃/s, respectively.

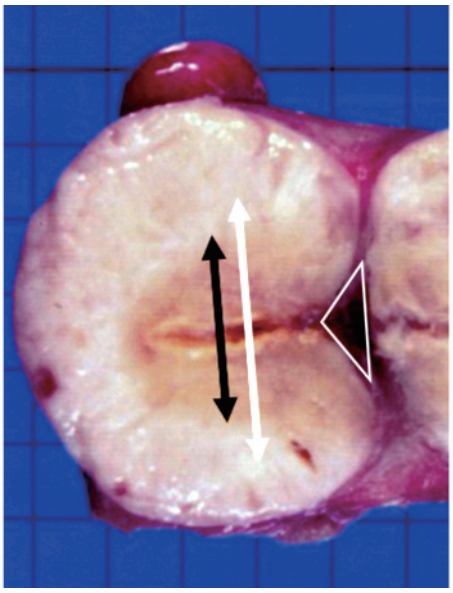

Figure 3. Section of the myoma including trace of puncture for microwave electrode.
Black arrow: charred area without carbonization. White arrow: coagulated width (white coagulation).
White open triangle: dimpling around the electrode.

dimpling was formed on the surface of the myoma around the electrode (Fig. 3).

Discussion

Glycerol is a naturally occurring molecule obtained through digestion of fat. Its infusion and ingestion have been utilized for over 80 years. Additionally, it has been used as an osmotic agent, infused intravenously for cerebral edema, for >40 years[4]. Moreover, it is commonly found as an ingredient in cosmetics[6], skin creams, ointments[7], enemas. Therefore, the infusion of a small amount of glycerol into the microwave irradiation site is deemed safe for clinical applications.

Glycerol can be safely used in the human body, and its physical characteristics make it ideal for MWA. Glycerol appears to be a suitable dielectric liquid when infused topically into the TCMM. To the best of our knowledge, this strategy to augment microwave heat generation in MWA has not been employed previously. The RDLF of glycerol increases up to three times that of water around 80℃ and then decreases slowly at temperatures exceeding 150℃ (Fig. 4). Glycerol can mix freely with water in the infused tissue and remains at the infused site during microwave irradiation, even after the vaporized water is removed by fractional distillation. Thus, stable heat generation is expected in the tissue at temperatures exceeding 100℃.

In this study, the TER was selected as a parameter for monitoring heat flow in the tissue, as it indicates the difference between the inflow or generation of heat and the outflow of heat at a point in the tissue. The infusion rate of glycerol or saline was adopted at 0.1 mL/min, because myoma tissue was so dense that infusible volume was extremely limited.

In the present study, when saline was infused at 70 W, temperature at 20 mm from electrode elevated soon after microwave irradiation started at TER of 0.075℃/s. Then, TER began to decrease to less than 0.018℃/s. Early rapid elevation of temperature may be caused by large RELF of water around 20℃ (Fig. 4) and boiling water near the electrode moved to peripheral tissue in addition to simple heat conduction. When glycerol was infused at 70 W, TER at 20 mm and 30 mm from electrode

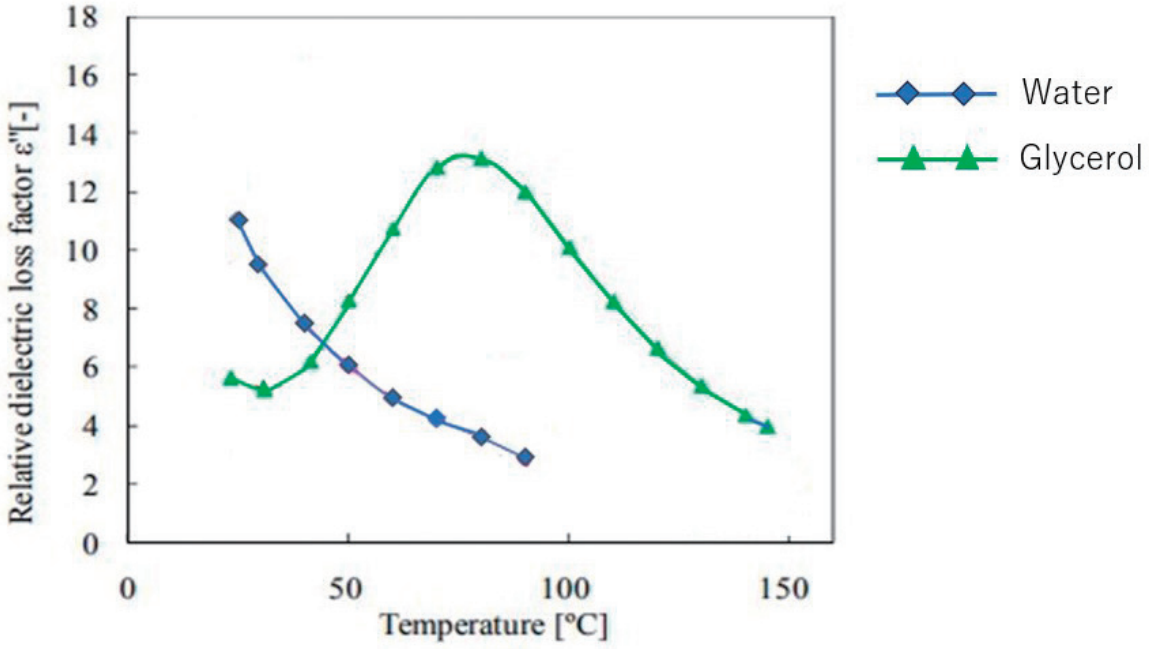

Figure 4. Temperature dependance of relative dielectric loss factors. Modified from reference 2 by Matsuzawa M.

surface was 0.045 and 0.025℃/s, respectively. The TER at 70 W with glycerol infusion was greater than that with saline infusion at 30 mm from the electrode. Moreover, tissue temperature at 30 mm with saline infusion was elevated by only 5.2℃ for 1200 s, while temperature was elevated by 19.8℃ at 30 mm with glycerol infusion. It appears that microwave irradiation with glycerol infusion generated more heat than with saline infusion. The total heat increase in the thin tissue 30 mm from the electrode provided by microwave irradiation with glycerol infusion was estimated to be approximately 3.8 (=19.8/5.2) times greater than that with saline infusion. This suggests that the infused glycerol continued the conversion of microwave energy to heat around the electrode during microwave irradiation.

This is the first paper reporting the results of an experimental study in which glycerol topically infused at a microwave irradiation site showed augmented heat generation during interstitial microwave irradiation. The authors believe that topical glycerol injection pretreatment increases the heat supply to the peripheral tissue and is applicable to overcome the heat sink caused by blood flow in the TCMM for vascular-rich myomas, instead of submyometrial injection of vasopressin[8].

Although the authors are not in a position to treat liver lesions, they noticed that the present simple experiment led them to an interesting working hypothesis. As liver tissue is soft and less fibrous than myomas, injecting glycerol in one shot and forming interstitial pooling around the electrode tip before MWA may be simpler. From reported tissue temperatures of the liver during interstitial microwave irradiation at 70 W, temperature at 5 mm rose rapidly during the initial 40 s[1] with TER 1.0℃/s. If TER had been maintained at 1.0℃/s for 200 s, temperature at 5 mm would have reached over 200℃. Actually, temperature was retained near 100℃ at 600 s. Animal and ex vivo experiments on microwave interstitial irradiation with glycerol injection in liver tissues may be worthwhile. Topical injection of glycerol may guide us to an unknown territory of the MWA in the liver.

In conclusion, topically infused glycerol around a microwave electrode tip enhances heat generation near irradiation site and provides augmented heat supply in the myoma tissue 30 mm away from microwave electrode. Topical glycerol infusion may enable MWA at temperatures exceeding 100℃.

This study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Osaka City University Graduate School of Medicine. Patient informed consent for the experimental use of a part of the surgical specimen was not necessary because all experiments in this study were performed in 2006, before February 2015 when the Ministry of Health, Labour and Welfare of Japan issued guidelines about experimental use of human subjects.

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All authors have no COI to declare regarding the present study.

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Associations between Parent-child Miscommunication about Suicidal Ideation in Children and Parental Anxiety/Depression

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Abstract

Background

Suicidal ideation is prevalent among children, and parental input is crucial in the comprehensive assessment process. However, the factors contributing to discrepancies between parents and children regarding perceptions of suicidal ideation remain poorly understood. In this study, we aimed to investigate the impact of parental anxiety/depression on parent-child miscommunication concerning suicidal ideation in children.

Methods

We conducted a cross-sectional study involving 108 children aged 9-17 years and their parents, who sought treatment at the neuropsychiatric outpatient clinic of Osaka Metropolitan University Hospital. Children's suicidal ideation and parental perception were assessed using an original interview and the Child Behavior Checklist. Parental anxiety/depression was measured using the 6-Items Kessler Scale (K6).

Results

Among the participants, 64 children (59.3%) exhibited suicidal ideation, and 52 parent-child pairs (48.1%) were categorized as the miscommunication group. The miscommunication group demonstrated significantly higher parental K6 scores, with the association reaching the optimal cut-off level of the K6.

Conclusions

To enhance the prognosis of children with suicidal ideation, more proactive parental interventions should complement the interventions provided to the children.

Key Words: Suicidal ideation; Miscommunication; Children; Parental anxiety/depression; Autism spectrum disorder

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Introduction

Suicidal ideation, as well as its clinical cases, is common in children[1-4]. Its clinical significance should be carefully evaluated, considering the potential for suicide attempts in children with suicidal ideation and those with underlying psychiatric disorders, which are regarded as critical predictors of the transition from suicidal ideation to suicide attempt[5,6]. Multifaceted interventions, similar to those employed to prevent suicide in adults, multifaceted interventions are vital to prevent suicide in children; however, evidence regarding effective methods for the early detection of suicidal ideation in children remains limited[7,8]. Discrepancies between parental perceptions and child psychiatric symptoms have been identified as factors that impede treatment efficacy, and reducing such discrepancies may lead to improved treatment outcomes[9]. Despite these considerations, the factors contributing to parent-child miscommunication regarding suicidal ideation in children remain largely unknown. Previous research has explored the association between parental depression and children's reporting of suicidal ideation[10-12], yielding inconsistent findings. Studies by Breton et al, Klimes-Dougan et al, and Kim et al observed variations in the reporting of suicidal ideation by children with parents who were depressed, with some cases being overreported, others underreported, and in some instances, no association with parental depression[13-15]. Additionally, Klaus et al, in a study of psychiatric inpatient adolescents, reported that parental history of depression was linked to agreement on suicidal tendencies[16]. In contrast, Jones et al reported that parental history of suicide attempts influenced children's awareness of suicidal ideation[17]. Currently, we lack a consensus on the relationship between parental depression, and child reports of suicidal ideation, and limited information exists on the specifics of parent-child miscommunication about this topic. Accordingly, we hypothesized that parental anxiety/depression may be associated with such miscommunication and conducted a cross-sectional study to validate this hypothesis.

Methods

Participants

In this study, we included 144 children (aged 9-17 years) consecutively referred to the psychiatric outpatient clinic of Osaka City University (currently known as Osaka Metropolitan University, Osaka, Japan) between April 2020 and March 2023. According to the exclusion criteria, children with intellectual disabilities (n=8; IQ <70 based on the Wechsler Intelligence Scale for Children-Third or Fourth Edition), those with acute psychotic or manic states (n=7), those with severe neurological impairments or refractory epilepsy (n=5), children without parents (n=6), those who did not provide assent/consent to participate in the study (n=10) were excluded, resulting in 108 children and their parents being included in the study.

Given the significant association between socioeconomic status and suicidal ideation[18-22], we conducted interviews to gather information on the absence of either the father or mother and family income. Additionally, trained clinicians diagnosed children with autism spectrum disorder (ASD) in the study. For family income, households receiving public assistance or having an annual income of less than 3 million yen (approximately 20000 United States dollars) were categorized as low-income households.

Measures

6-Item Kessler Scale

The 6-Items Kessler Scale (K6) contained six questions for participants with a score of 0-4, with a total score of 24[23]. Parents were asked to rate how often they have felt "nervous", "hopeless", "restless or fidgety", "so depressed that nothing could cheer you up", "that everything was an effort", and "worthless" during the past 30 days. Parents responded with the following options: "0 − none of the time", "1 − a little time of the time", "2 − some of the time", "3 − most of the time", and "4 − all the time". The K6 has excellent reliability and validity as a screening tool for psychological distress and is suitable for screening mood and anxiety disorders[23,24]. The Japanese version of the K6 used in the World Mental Health Survey demonstrated optimal performance similar to that of the original version[25]. Sakurai et al proposed an optimal cut-off score of 4/5 for mood/anxiety disorders in the Japanese version of the K6[26].

Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version

The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children — Present and Lifetime Version (K-SADS-PL), a semi-structured interview designed to assess current and past episodes of psychopathology in children and adolescents, was administered to the parents. The psychometric properties of the K-SADS-PL have been estimated to be excellent in prior studies, with high inter-rater (κ=0.93) and test-retest (intraclass correlation coefficients ranging from 0.74-0.90) reliability[27]. Each item is scored as present, absent, or unknown. The diagnostic algorithm was implemented according to international guidelines. We used the Japanese version of the K-SADS-PL-J, which has consistently demonstrated good interrater reliability and high concurrent validity across studies[28].

Child Behavior Checklist

The Child Behavior Checklist (CBCL), a parent-reported standardized rating scale, was utilized to assess broad childhood psychopathology. The CBCL consists of 113 questions[29], with parents rating each item on a 3-point scale [0, not true (as far as the reporter knows); 1, somewhat or sometimes true; and 2, very often or often true]. It includes three domains (total, internalizing, and externalizing scores) and eight subscales (withdrawal, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior). T scores of these three domains and eight subscales were calculated using a standardized distribution of Japanese children[30].

Assessment of children's suicidal ideation

To assess children's suicidal ideation, we interviewed participants by asking, "Have you ever wanted to commit suicide?" Participants who responded, "I don't want to kill myself, but I sometimes want to die" or "I sometimes want to kill myself", were considered to have suicidal ideation.

Definition of the parent-child miscommunication about suicidal ideation in children

Item 91 of the CBCL was used to assess the parents' understanding of their children's suicidal ideation [In the present or past six months: (your child) talks about killing self; 0 = not applicable, 1 = somewhat or sometime applicable, 2 = applicable]. Parents who scored 1 or 2 thought that their children had suicidal ideation and talked to them about suicide. Parents and children with discrepancies between their answers and the presence or absence of suicidal ideation in their children were assigned to the miscommunication group. In contrast, parents and children who agreed were assigned to the control group, i.e., those in which the children had no suicidal ideation and the parent scored 0, or those in which the children had suicidal ideation and the parent scored 1 or 2.

Diagnosis of ASD

For all participants, we conducted comprehensive life history interviews with parents, interviews with both parents and children by clinicians, and observations of children's symptoms by several child psychiatrists. Based on this information, ASD diagnosis was confirmed through a multidisciplinary team conference in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM) -5 diagnostic criteria.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 28.0.1.0; IBM Corp., Armonk, NY, USA). Fisher's exact test was used to compare the categorical variables between the miscommunication and control groups. The Mann-Whitney U-test was used to compare continuous variables in the evaluation of the measured data. Associations of the K6 scores of the miscommunication group parents were estimated using binominal logistic regression models after controlling for other factors that had statistically significant differences between the groups in the univariate analysis or were considered potential confounders. A two-sided p-value <0.05 was considered statistically significant for all tests.

Ethics approval and informed consent

All the children and their parents provided written informed assent/consent before participation. The study was approved by the Institutional Review Board at the Graduate School of Medicine, Osaka Metropolitan University (approval number 2021-009) , and conducted in accordance with the principles of the Declaration of Helsinki and its later amendments.

Results

Of the total participants, 64 children (59.3%) exhibited suicidal ideation, whereas 52 pairs of parents and children (48.1%) were classified as the miscommunication group. This miscommunication group comprised 48 pairs (92.3%) of "parents do not perceive that their children talk about suicide even though their children have suicidal ideation" and four pairs (7.7%) of "parents perceive that their children talk about suicide even though their children do not have suicidal ideation". The control group consisted of 16 pairs (28.6%) of "the child has suicidal ideation, and the parents think the child talks about suicide" and 40 pairs (71.4%) of "the child has no suicidal ideation, and the parents do not think the child talks about suicide". Participants who were identified as having suicidal ideation based on our assessment had significantly higher T-scores for anxiety/depression on

Table 1. Participants' sociodemographic characteristics

	Total (n=108)	Miscommunication (n=52)	Control (n=56)	U	p
Sex, male, n(%)	43 (39.8%)	21 (40.4%)	22 (39.3%)	N/A[a]	1.000
female, n(%)	65 (60.2%)	31 (59.6%)	34 (60.7%)		
Age (years)	13.4±1.8	13.7±1.5	13.1±2.1	1668.0[b]	0.192
Single parent, n(%)	18 (16.7%)	8 (15.4%)	10 (17.9%)	N/A[a]	0.800
Low income, n(%)	17 (15.7%)	9 (17.3%)	8 (14.3%)	N/A[a]	0.793
Autism spectrum disorder, n(%)	72 (66.7%)	32 (61.5%)	40 (71.4%)	N/A[a]	0.312

Notes: Values are presented as the mean±standard deviation unless otherwise noted. [a]Fisher's exact test; [b]Mann-Whitney U test.

Abbreviations: N/A, not applicable.

Table 2. K-SADS-PL diagnoses for the miscommunication and control groups

	Total (n=106)	Miscommunication (n=51)*1	Control (n=55)*2	p
Mood disorders, n(%)	57 (53.8%)	30 (58.8%)	27 (49.1%)	0.336
Major depressive disorder	21 (19.8%)	9 (17.6%)	12 (21.8%)	0.633
Dysthymia	0 (0%)	0 (0%)	0 (0%)	1.000
Adjustment disorder	35 (33.0%)	21 (41.2%)	14 (25.5%)	0.101
Bipolar disorder	2 (1.9%)	0 (0%)	2 (3.6%)	0.496
Psychotic disorders	8 (7.5%)	4 (7.8%)	4 (7.3%)	1.000
Anxiety disorders	42 (39.6%)	23 (45.1%)	19 (34.5%)	0.322
Panic disorder	7 (6.6%)	4 (7.8%)	3 (5.5%)	0.709
Separaton-anxiety disorder	0 (0%)	0 (0%)	0 (0%)	1.000
Social anxiety disorder	19 (17.9%)	11 (21.6%)	8 (14.5%)	0.449
Generalized anxiety disorder	21 (19.8%)	9 (17.6%)	12 (21.8%)	0.633
Obessive-compulsive disorder	4 (3.8%)	1 (2.0%)	3 (5.5%)	0.619
Posttraumatic stress disorder	1 (0.9%)	0 (0%)	1 (1.8%)	1.000
Specific phobia	14 (13.2%)	11 (21.6%)	3 (5.5%)	**0.020**
Enuresis	0 (0%)	0 (0%)	0 (0%)	1.000
Encopresis	0 (0%)	0 (0%)	0 (0%)	1.000
Eating disorders	11 (10.3%)	4 (7.8%)	7 (12.7%)	0.530
Behavioral disorders	20 (18.9%)	9 (17.6%)	11 (20.0%)	0.808
Attention-deficit/hyperactivity disorder	11 (10.3%)	5 (9.8%)	6 (10.9%)	1.000
Oppositional defiant disorder	10 (9.4%)	5 (9.8%)	5 (9.1%)	1.000
Conduct disorder	5 (4.7%)	2 (3.9%)	3 (5.5%)	1.000
Tic disorders	12 (11.3%)	3 (5.9%)	9 (16.4%)	0.126
Tic disorder	9 (8.5%)	2 (3.9%)	7 (12.7%)	0.164
Tourette disorders	3 (2.8%)	1 (2.0%)	2 (3.6%)	1.000
Substance abuse	0 (0%)	0 (0%)	0 (0%)	1.000

Notes: Values are presented as numbers (%). Statistically significant differences ($p<0.05$) are indicated in bold font. Fisher's exact test. *1One in Miscommunication group and *2one in control group did not complete K-SADS-PL.

Abbreviations: K-SADS-PL, the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version.

Table 3. CBCL T scores for the miscommunication and control groups

	Miscommunication (n=50)*1	Control (n=54)*2	U	p
Total problems	65.8±9.5	64.6±8.4	1450.0	0.515
Internalizing	68.4±10.5	67.8±9.5	1442.5	0.547
Externalizing	59.7±10.3	57.8±8.9	1451.0	0.510
Withdrawn	66.2±9.8	65.6±9.4	1336.0	0.917
Somatic complaints	65.3±10.1	66.1±10.5	1323.5	0.862
Anxious/Depressed	66.6±11.8	65.1±11.4	1466.0	0.450
Social problems	59.7±8.6	59.1±7.9	1377.0	0.859
Thought problems	60.0±12.6	61.4±11.8	1277.5	0.620
Attention problems	58.7±9.4	61.1±8.7	1076.5	0.072
Delinquent problems	58.0±9.4	58.0±8.8	1345.0	0.973
Aggressive behaviors	59.7±9.3	58.1±6.8	1457.5	0.482

Notes: Values are presented as mean±standard deviation. Mann-Whitney U-test. *1Two in the Miscommunication group and *2two in the control group did not complete CBCL.

Abbreviations: CBCL, Child Behavior Checklist.

Table 4. Comparison of the K6 scores of parents between the miscommunication and control groups

	Miscommunication (n=52)	Control (n=56)	U	p
K6 score, mean±SD	7.48±6.44	4.95±5.15	1818.0[a]	**0.025**
0≦K6≦4	19 (36.5%)	35 (62.5%)	N/A[b]	**0.012**
5≦K6	33 (63.5%)	21 (37.5%)		

Notes: Values are presented as mean±standard deviation or number (%). Statistically significant differences ($p<0.05$) are indicated in bold font. [a]Mann-Whitney U-test; [b]Fisher's exact test.

Abbreviations: K6, Kessler 6 scale; SD; standard deviation; and N/A, not applicable.

Table 5. Results of binary logistic regression analysis showing predictors of total K6 scores in the miscommunication group (n=106)

Independent Variable	B	SE	Wald	p	Exp (B)	95% CI for Exp (B) Lower	Upper
Parental K6 score	0.087	0.037	5.515	**0.019**	1.090	1.014	1.172
Age(years)	0.198	0.119	2.755	0.097	1.219	0.965	1.539
Sex, male	0.642	0.484	1.764	0.184	1.901	0.737	4.906
Children's ASD	−0.927	0.495	3.503	0.061	0.396	0.150	1.045
Children's Mood Disorders	0.510	0.427	1.423	0.233	1.665	0.721	3.845
Children's Anxiety Disorders	0.602	0.435	1.918	0.166	1.826	0.779	4.282
Constant	−3.382	1.694	3.989	0.046	0.034		

Notes: Statistically significant differences ($p<0.05$) are indicated in bold. Two patients who did not complete the K-SADS-PL were excluded from the analysis.

Abbreviations: K6, Kessler 6 scale; SE, standard error; CI, confidence interval; and ASD, autism spectrum disorder.

the CBCL and a significantly higher prevalence of mood disorders on the K-SADS-PL than those without suicidal ideation, showing certain construct validity of the methods regarding psychometric properties. (58.7 vs 42.9, $p<0.01$, Mann-Whitney U test; 63.5% vs 39.5%, $p=0.018$, Fisher's exact test, respectively). A comparison of sociodemographic characteristics between the two groups is presented in Table 1. No significant differences were observed between the groups in terms of sex, age, single-parent status, low income, and ASD prevalence in the children. Specific phobia was notably more prevalent in the miscommunication group compared to the control group (21.6% vs 5.5%, $p=0.020$; Table 2). However, we observed no significant differences in CBCL T scores for both groups (Table 3).

The mean parental K6 scores were significantly higher in the miscommunication group than in the control group (7.48 vs 4.95, $p=0.025$). Moreover, the miscommunication group exhibited a significantly higher percentage of K6 scores ≧5, which is considered the optimal cut-off in Japan, compared with that in the control group (63.5% vs 37.5%, $p=0.012$; Table 4).

To explore the factors associated with miscommunication, binomial logistic regression analysis was conducted, with the presence of miscommunication as the dependent variable and parental K6 score, age, sex, presence of ASD, presence of children's mood disorders, and presence of children's anxiety disorders (items that were considered potential confounders) as independent variables (Table 5). The miscommunication was predicted using parental K6 scores. For each one-point increase in parental K6 score, the likelihood of miscommunication increased by 1.090 points.

Discussion

To the best of our knowledge, this is the first study to demonstrate a link between parental anxiety/depression and parent-child miscommunication about suicidal ideation in children. Even after adjusting for children's age, sex, mood/anxiety disorders, and ASD, the association remained significant. The prevalence of suicidal ideation in children is typically between 6%-28%; however, studies have been conducted in general population samples or clinical cases, or in various countries and regions, with different methodologies and study samples[1-4,11,31]. Studies focusing exclusively on children with ASD report even higher rates, with some showing suicidal ideation in 72% of such children[20]. The study sample included a substantial proportion (59.3%) of children with suicidal ideation, likely influenced by the high prevalence of ASD among the participants. Given the predictive link between depression or anxiety disorder and suicide attempts, the high prevalence of suicidal ideation in clinical cases underscores the importance of early detection and intervention[5,6]. The key finding of this study is the significance of parental anxiety/depression in contributing to miscommunication about children's suicidal ideation, independent of the children's characteristics[7,8].

Prior research has also suggested an association between parental depression and suicidal ideation in children[10-12], consistent with the higher proportion of children with suicidal ideation in the miscommunication group, which had significantly higher parental anxiety/depression. Notably, while children's mood disorders/anxiety disorders did not significantly contribute to miscommunication, parental anxiety/depression remained associated with it, irrespective of the child's condition. The miscommunication group, comprising 48.1% of the total, aligns with the findings of previous studies exploring parental awareness of suicidal ideation in their children[14,17]. The miscommunication primarily consisted of cases where parents were unaware of their children's suicidal ideation, reflecting the difficulty in openly discussing such feelings with parents[13,31]. Furthermore, parental depression has been linked to discrepancies in symptom reporting in children, including anxiety disorders[32] and our study demonstrates the association between miscommunication and parental depression at the K6 score cut-off level[26]. Assuming a cutoff of 4/5 for K6, 31.3% of the community sample fell into the category of 5 points or higher[26]. In our study, 50.0% of parents scored 5 or higher, and it is expected that a larger percentage of parents of children in clinical cases will score 5 or higher than in the community sample. For mood and anxiety disorders, the K6 has a sensitivity of 100% and specificity of 68.7% at a cutoff of 4/5 points[26], which includes a certain number of parents with no clinically diagnosed mood or other disorders. While it may be difficult to assume that miscommunication between parents and children occurs when clinicians cannot find obvious signs of mood or anxiety disorders in parents, the present study suggests that the K6 provides a sensitive measure of miscommunication about a child's rarefied thoughts.

Discrepancies in perceiving a child's symptoms and behavior may hinder treatment effectiveness, emphasizing the importance of obtaining information from multiple sources[9]. We have shown that parental depression, even when it is below the clinical threshold, is associated with parent-child miscommunication regarding suicidal ideation, suggesting proactive therapeutic intervention may improve the child's prognosis.

Children with ASD face a higher risk of suicidal ideation, with comorbid anxiety and depression contributing to this association[18,20,33,34]. However, their thoughts and feelings are not well expressed, and their mood and suicidal ideation have not been adequately discussed, thereby confounding the accurate diagnosis of mood disorders and suicidal ideation[35,36]. Based on the results of these previous

studies, we expected a higher prevalence of ASD in the miscommunication group; however, there was no significant difference between the two groups. The presence of psychiatric comorbidity, particularly social anxiety disorder, is common in children with ASD[37,38]. The inclusion of clinical cases in our study may have facilitated more intense communication between parents and children with ASD, who were likely to have more comorbidities and anxiety complaints than non-ASD children, potentially leading to the relatively low proportion of ASD children in the miscommunication group.

The prevalence of suicidal ideation among children and adolescents increases with age[1,2]. Zaborskis et al suggested that conversation duration between parents and children decreases with age in adolescents[39]. Older age in children may contribute to miscommunication with parents, which could partially explain the older age of children in the miscommunication group besides the prevalence of suicidal ideation.

This study had several limitations. The relatively small sample size of outpatient clinical cases at a single medical facility may limit the generalizability of the results. However, our institution accepts various patients consecutively under Japan's universal health insurance system, reducing the sampling bias to some extent. Second, as this study is a cross-sectional study, we could not establish a causal relationship between parental depression/anxiety and parent-child miscommunication about suicidal ideation in children. Third, we assessed the children's suicidal ideation using an original interview. However, children with suicidal ideation assessed by our method had significantly higher CBCL T scores regarding anxiety/depression and a significantly higher prevalence of mood disorders as assessed by the K-SADS-PL than those without suicidal ideation. Paul et al suggested that CBCL T-scores for anxiety and depression are associated with suicidal ideation in children[40]. Therefore, construct validity was ensured. Fourth, we could not examine two subgroups, "parents do not perceive that their children talk about suicide even though their children have suicidal ideation" and "parents perceive that their children talk about suicide even though their children do not have suicidal ideation" within the miscommunication group individually owing to a limited number of cases. As noted above, there was a trend toward higher parental K6 scores in the latter subgroup; however, it would be difficult to draw statistically meaningful conclusions with a limited number of patients. Studies in this area are limited, and those dealing with clinical cases are particularly valuable. Therefore, further large-scale studies based on these findings are warranted. Finally, we used the DSM-Ⅳ-Text Revision-based K-SADS-PL because the DSM-5-based version has not yet been standardized in Japanese.

In conclusion, we confirmed that parental K6 scores were associated with parent-child miscommunication about suicidal ideation in children at the cut-off level, indicating a possible need for proactive intervention, even for parents without a clinical diagnosis of depression. It is easy to assume that there is miscommunication between parent and child if the parent is depressive in the clinician's examination, but otherwise it is difficult to determine whether there is miscommunication between parent and child. K6 can acutely detect miscommunication between parents and children, which may help clinicians make better decisions. Further studies to examine the content of miscommunication individually and to determine which types of miscommunication are more suitable for detection by the K6 will contribute to the early detection of suicidal ideation in children.

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Relationship of Internet Addiction with Affective Temperament and Occupational Stress among Japanese Workers: A Cross-sectional Study

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Abstract

Background

We aimed to clarify the relationship between internet addiction (IA) with affective temperament and occupational stress among Japanese workers.

Methods

We conducted a cross-sectional online survey in Japan and included 1005 eligible participants in the final analysis. We used the Young's Diagnostic Questionnaire for IA, a self-administered screening test for internet dependence. In addition, temperament was assessed using the full version of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego auto questionnaires. Occupational stress was assessed using the Generic Job Stress Questionnaire. Multiple logistic regression analysis was performed to estimate odds ratios (ORs) for demographic and work-related variables, the five temperaments, and six Generic Job Stress Questionnaire subscales for the IA group.

Results

IA was associated with hyperthymic temperament (OR=1.12; 95% Confidence Interval (CI), 1.05-1.20), irritable (OR=1.22; 95% CI, 1.13-1.32) and anxious temperament (OR=1.13; 95% CI, 1.06-1.21), moderate job control (OR=2.12; 95% CI, 1.10-4.08), and low social support from coworkers (OR=2.59; 95% CI, 1.25-5.39).

Conclusions

This study demonstrated the relationships between IA and hyperthymic, irritable, and anxious temperaments, as well as that with moderate job control and low social support from coworkers. Workers may manage their internet use better by understanding their own affective temperament, seeking help from coworkers, and managing job control. For example, cognitive behavior therapy, mindfulness, and frequent face-to-face contact may be useful.

Key Words: Internet addiction; YDQ; Affective temperament; TEMPS-A; GJSQ

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Introduction

The internet is an indispensable tool nowadays. Rapid technological developments and the proliferation of wireless connections facilitate internet use. However, while the internet has certain positive effects on human development, its overuse, commonly known as internet addiction (IA), has become a serious behavioral health problem worldwide[1]. IA is defined as an excessive and uncontrollable preoccupation or impulse with the internet, which can cause various life problems[2].

To delve deeper into this issue, several studies have investigated the prevalence of IA, considering various demographic differences. A previous meta-analysis focused on students reported a prevalence of IA of about 7% worldwide. Conversely, some studies have focused exclusively on adults. In Japan, the prevalence of mild or severe IA was 19.0% in large cities, 13.1% in middle cities, and 12.1% in small municipalities[3]. In another study, approximately 5% of school personnel in rural areas in Japan were at risk for IA[4]. In Taiwan, approximately 4.1% of information technology engineers had pathological internet use[5].

In contrast to the study of IA, which focuses on behavior and prevalence, temperament is a distinct concept and an inherent bias in a person's views and behavior that makes them prone to certain behaviors[6]. Temperament is considered the biological basis of personality development[7]. Akiskal proposed the five affective temperaments by adding an anxious type to the depressive, cyclothymic, hyperthymic, and irritable basic states proposed by Kraepelin[8]. The affective temperament is said to be stable for ≧6 years[9]. Numerous studies have reported the relationship between temperament and mental problems[10-12]. For instance, in students, a relationship between IA and the five affective temperaments, particularly anxious temperament, has been reported[13]. Compared with students, workers who have occupational stress cannot be ignored, as internet use in the workplace ranges from aimless surfing to off-the-job use for personal purposes. Between 30% and 50% of workplace internet use is nonwork related, resulting in an annual loss of $1 billion[14]; an employee spends at least one hour in off-the-job activities during a regular working day[15]. Therefore, we aimed to clarify the relationship between IA and affective temperament among workers, not students or young adults.

In addition, there are reports on the relationships between workers' temperament and depressive symptoms[16,17] and insomnia[18]. Moreover, previous meta-analysis and systematic reviews demonstrated the relationship between occupational stress and burnout[19,20] or depression[20,21], while a previous study reported that high job strain was associated with an increased risk of IA and that high work social support reduced the risk of IA[5].

Based on these findings, we hypothesized that workers' affective temperament and some types of occupational stress might influence IA. Thus, we aimed to clarify the relationship of IA with affective temperament and occupational stress among workers.

Methods

Study design, participants, and procedure

On December 16-17, 2020, the research firm Macromill, Inc. Japan conducted a cross-sectional online survey in Japan. The target population included Japanese residents who were employed and aged 20-65 years. Data from 1030 Japanese workers with various employment statuses were collected from among the about 10 million people registered with Macromill, Inc., after excluding the participants with at least one missing entry, 1005 eligible participants were included in the final analysis. Using this survey data, we previously reported the relationships between occupational

stress, changes in the work environment during the COVID-19 pandemic, and depressive and anxiety symptoms among nonhealthcare workers[22]. Participants were informed that participation was voluntary. Informed consent was obtained from all participants, and it was guaranteed that the researchers would not have access to Macromill's personal information (name, phone number, home address, etc.). Macromill points, original point service of Macromill Inc., were distributed to all participants, and participants could exchange these points for prizes or cash.

Ethics

The study was conducted in compliance with the Declaration of Helsinki and its future amendments. The study plan was approved by the Ethics Committee of Osaka City University (authorization number 4245). All data were stored exclusively in our database; participants' employers and affiliations had no access to the data and could not know who participated.

Demographic information

Participants provided demographic information such as age, sex, marital status, presence of children, and education. We also collected information on work-related variables such as occupation, employment status, job classification, work type, and frequency of telecommuting.

Measures of IA

The Young's Diagnostic Questionnaire (YDQ) for IA is a self-administered screening test for internet dependence developed as an 8-item diagnostic questionnaire based on diagnostic criteria for pathological gambling from the Diagnostic and Statistical Manual of Mental Disorders Ⅳ[23]. It is a yes/no questionnaire type, and can be completed in about 5 min. It consists of the following items: "internet obsession", "tolerance (prolonged time)", "difficulty in controlling", "withdrawal", "longer time than originally thought", "negative social effects", "lying", and "escapist use". The specifics are shown in Table 1. The higher the total score between 0 and 8, the higher the level of dependence, with "yes" being scored as 1 and "no" as 0. Given the lack of consensus on formal diagnostic criteria for IA, a score ≧5 was considered to indicate IA[23] and the YDQ was also used in previous IA studies with adults[24]. A score ≧5 was used as cutoff to separate participants into IA and non-IA groups.

Measures of temperament

Temperament was assessed using the full Japanese version of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego auto questionnaire (TEMPS-A)[25], of confirmed reliability and

Table 1. Young's Diagnostic Questionnaire for internet addiction (YDQ)

1	Do you feel preoccupied with the Internet (think about previous online activity or anticipate next online session)?
2	Do you feel the need to use the Internet with increasing amounts of time in order to achieve satisfaction?
3	Have you repeatedly made unsuccessful efforts to control, cut back, or stop Internet use?
4	Do you feel restless, moody, depressed, or irritable when attempting to cut down or stop Internet use?
5	Do you stay online longer than originally intended?
6	Have you jeopardized or risked the loss of significant relationship, job, educational or career opportunity because of the Internet?
7	Have you lied to family members, therapist, or others to conceal the extent of involvement with the Internet?
8	Do you use the Internet as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)?

Reference, Young KS. Internet addiction: The emergence of a new clinical disorder. Cyberpsychol Behav 2007;10: 671-679.

validity[26]. The TEMPS-A is a yes/no self-report questionnaire that assesses temperament consisting of 110 items classified into five temperament types: depressive, cyclothymic, hyperthymic, irritable, and anxious. For example, one of the questions related to depressive temperament is “I am a sad, unhappy person”. ; cyclothymic temperament is “I normally need more than 9h of sleep”. ; hyperthymic temperament is “I am usually in an upbeat or cheerful mood”. ; irritable temperament is “I am usually in an upbeat or cheerful mood”. ; and anxious temperament is “I am by nature a dissatisfied person”. Higher scores indicate a stronger temperament.

Measures of occupational stress

Occupational stress was assessed using the Generic Job Stress Questionnaire (GJSQ) developed by the National Institute for Occupational Safety and Health (NIOSH)[27]. The Japanese version of the GJSQ has demonstrated adequate reliability and validity[28,29]. Based on the NIOSH Occupational Stress Model[27], we focused on the four subscales of occupational stress assessment (job demand, job control, variance in workload, and job future ambiguity) to assess occupational stress. For example, one of the questions related to job demand is “How much work load do you have?”; job control is “How much influence do you have over the variety of tasks you perform?”; variance in workload is “How often is there a marked increase in the work load?”; and job future ambiguity is “How certain are you about what your future career picture looks like?” Two subscales were used to assess social support (from supervisors and coworkers). For example, one of the questions related to social support (from supervisors and coworkers) is “How much do each of these people go out of their way to do things to make your work life easier for you?” It acts as a buffer based on previous findings on the relationships between psychological symptoms and occupational stress[18]; the GJSQ items of job control and social support had a positive direction, with higher scores indicating lower stress levels. In contrast, the other items were negatively oriented, with higher scores indicating higher stress levels.

Statistical analyses

Using the cutoff point, participants were divided into IA and non-IA groups, with the inclusion criteria for the IA group defined as the dependent variables and the demographic variables, work-related variables, five temperaments, and six GJSQ subscales as independent variables. Univariate and multiple logistic regression analysis were performed to estimate odds ratios (ORs) for demographic and work-related variables, the five temperaments, and six GJSQ subscales in the IA group; ORs were calculated using the IA group as the dependent variable and demographic variables, work-related variables, five temperaments, and six subdivided GJSQ subscales as independent variables. GJSQ subscales were classified into low, medium, and high categories according to their tertile values. Statistical significance was set at $p < 0.05$. We used SPSS version 28.0 software (SPSS Inc., Chicago, IL) for all statistical analyses. In these analyses, we did not impute missing responses on the variables.

Results

Table 2 shows the participants’ characteristics. The mean age was 46.1±10.7 years. There were 744 men (74.0%) and 261 women (26.0%). Of these, 371 (36.9%) were unmarried and 634 (63.1%) married, and 562 (55.9%) had children. Regarding work-related variables, 812 (80.8%) were regular workers, 576 (57.3%) were nonmanagers, 833 (82.9%) were day workers, and 736 (73.2%) were present at the workplace every day. Table 3 shows the subjects’ YDQ, TEMPS-A, and GJSQ scores. The mean YDQ score was 1.7 (Standard Deviation (SD)=2.0) and 134 (13.3%) participants were considered to

have IA. Table 4 shows the results of the univariate and multiple logistic regression analysis. In a multiple logistic regression analysis, IA was associated with hyperthymic (OR=1.12; 95% CI, 1.05-1.20), irritable (OR=1.22; 95% CI, 1.13-1.32) or anxious temperament (OR=1.13; 95% CI, 1.06-1.21); age 50-60 years (OR=0.26; 95% CI, 0.09-0.73); moderate job control (OR=2.12; 95% CI, 1.10-4.08); and low social support from coworkers (OR=2.59; 95% CI, 1.25-5.39).

Table 2. Participants' characteristics (n=1005)

	n (%), Mean±SD
Age (years)	46.1±10.7
20-29	80 (8.0)
30-39	199 (19.8)
40-49	310 (30.8)
50-59	304 (30.2)
≥ 60	112 (11.1)
Gender	
Male	744 (74.0)
Female	261 (26.0)
Marital status	
Married	634 (63.1)
Single	371 (36.9)
Child (ren)	
None	443 (44.1)
≥ 1	562 (55.9)
Education (years)	
≦ 12	231 (23.0)
≥ 13	774 (77.0)
Occupation	
Clerical worker	286 (28.5)
Technical worker	251 (25.0)
Workers (not clerical and technical)	262 (26.1)
Civil servants	70 (7.0)
Executives	31 (3.1)
Self-employment	105 (10.4)
Type of employment	
Regular	812 (80.8)
Temporary	193 (19.2)
Position classification	
Non-manager	576 (57.3)
Manager	429 (42.7)
Work pattern	
Daytime	833 (82.9)
Shift	172 (17.1)
Frequency of working at home	
None (everyday at workplace)	736 (73.2)
≦ Twice per week	121 (12.0)
>3 times per week	148 (14.7)

Abbreviations: SD, standard deviation.

Table 3. Participants' YDQ score, anxiety symptoms, temperaments, GJSQ scores (n=1005)

	Range	Mean (SD)	n (%)
YDQ score	0-8	1.7 (2.0)	
≧ 5 Internet Addiction			134 (13.3)
≦ 4 Non-Internet Addiction			871 (86.7)
Temperaments			
Depressive	0-20	9.0 (4.0)	
Cyclothymic	0-21	6.8 (4.9)	
Hyperthymic	0-20	6.6 (4.3)	
Irritable	0-21	5.7 (4.3)	
Anxious	0-26	7.5 (6.1)	
GJSQ scores			
Job demand	11-55	34.4 (6.3)	
Job control	16-80	47.6 (10.8)	
Job future ambiguity	4-20	17.3 (5.3)	
Variance in workload	3-15	9.3 (2.4)	
Supervisors' support	4-20	12.8 (3.8)	
Coworkers' support	4-20	13.4 (3.6)	

GJSQ, generic job stress questionnaire; YDQ, young's diagnostic questionnaire for internet addiction Score; and SD, standard deviation.

Discussion

This study demonstrated the relationship between IA and hyperthymic, irritable, and anxious temperaments as well as with moderate job control and low social support from coworkers. This study aimed to identify relationship of IA with affective temperament and occupational stress among Japanese workers.

Affective temperament and IA

A previous study among Turkish students revealed the relationship between IA and hyperthymic temperament[13]. However, such relationship was not observed among Lebanese young adults[30]. The present results are consistent with the former[13] but not with the latter[30]. Our study is in agreement with both the previous studies which revealed a relationship between IA and irritable and anxious temperament[13,30].

Hyperthymic temperament is associated with positive traits such as being bright, fun-loving, outgoing, cheerful, optimistic, confident, full of ideas, eloquent, active, sleeping less but being tireless, and a taste for leadership. Although considered a protective factor against anxiety disorders, bipolar disorder, substance abuse, impulse control disorders[12], and against suicide in patients with unipolar and bipolar disorders[10], it is associated with single-mindedness, risk-taking, and not admitting to much meddling on one's part[25]. Risk-taking encompasses behaviors that are performed under uncertainty without robust contingency planning[31], and may frequently lead to negative consequences[32]. Lane et al showed that the fear of uncertainty is positively correlated with smartphone addiction[33]. The risk-taking associated with the hyperthymic temperament may lead to internet dependence. The results of the Lebanese study differed significantly from our study, which may be due to the different demographic characteristics of their participants: a lower average age (22.25±2.87 years) and 70.9% female ratio[30]. Although irritable temperament has two intellectual virtues, skeptical and critical, it is the darkest temperament: complaining, grumpy, angry, frustrated, sexually jealous, and violent[25]. In addition, it negatively correlates with a preference for being with

Table 4. Univariate and Multiple logistic regression analysis of risk factors belonging for the IA group compared for the non-IA group

	Univariate Model			Adjusted Model†		
	OR	(95% CI)	p	OR	(95% CI)	p
Age (years)						
(20-29)	Ref			Ref		
30-39	1.07	(0.56-2.04)	0.837	0.59	(0.24-1.47)	0.254
40-49	0.54	(0.28-1.04)	0.063	0.40	(0.15-1.02)	0.055
50-59	0.44	(0.23-0.85)	0.015	0.26	(0.09-0.73)	0.011
≥60	0.35	(0.14-0.83)	0.018	0.27	(0.07-1.03)	0.056
Gender						
(Male)	Ref			Ref		
Female	1.10	(0.73-1.66)	0.642	0.97	(0.48-1.97)	0.933
Marital status						
(Married)	Ref			Ref		
Single	1.06	(0.72-1.54)	0.778	0.69	(0.34-1.38)	0.292
Child(ren)						
(None)	Ref			Ref		
≥ 1	1.08	(0.74-1.55)	0.699	1.39	(0.71-2.73)	0.334
Education (years)						
(≦12)	Ref			Ref		
≥ 13	0.94	(0.62-1.44)	0.791	0.87	(0.48-1.60)	0.660
Occupation						
(Clerical worker)	Ref			Ref		
Technical worker	1.17	(0.73-1.87)	0.521	1.24	(0.64-2.40)	0.527
Workers (not clerical and technical)	0.83	(0.51-1.37)	0.466	0.68	(0.34-1.35)	0.268
Civil servants	1.24	(0.61-2.50)	0.555	1.20	(0.44-3.26)	0.721
Executives	0.41	(0.10-1.79)	0.237	0.34	(0.05-2.47)	0.284
Self-employment	0.36	(0.15-0.88)	0.025	0.30	(0.09-1.02)	0.055
Type of employment						
(Regular)	Ref			Ref		
Temporary	0.62	(0.37-1.04)	0.071	0.67	(0.30-1.50)	0.332
Position classification						
(Non-manager)	Ref			Ref		
Manager	1.03	(0.71-1.49)	0.881	1.76	(0.99-3.12)	0.055
Work pattern						
(Daytime)	Ref			Ref		
Shift, other	1.13	(0.71-1.81)	0.611	1.07	(0.56-2.05)	0.837
Frequency of working at home						
(None (everyday at workplace))	Ref			Ref		
≦ Twice per week	0.96	(0.54-1.69)	0.882	0.66	(0.31-1.43)	0.293
> 3 times per week	0.82	(0.47-1.41)	0.466	1.11	(0.53-2.33)	0.784
Temperaments						
Depressive	1.22	(1.17-1.28)	<0.001	0.92	(0.84-1.00)	0.051
Cyclothymic	1.27	(1.21-1.32)	<0.001	1.07	(0.99-1.15)	0.099
Hyperthymic	1.17	(1.12-1.22)	<0.001	1.12	(1.05-1.20)	0.001
Irritable	1.39	(1.32-1.46)	<0.001	1.22	(1.13-1.32)	<0.001
Anxious	1.23	(1.18-1.27)	<0.001	1.13	(1.06-1.21)	<0.001
Occupational stress						
Job Demand						
(Low)	Ref			Ref		
Moderate	1.40	(0.89-2.22)	0.146	1.20	(0.61-2.34)	0.597
High	0.95	(0.59-1.53)	0.832	0.68	(0.33-1.43)	0.315
Job Control						
(High)	Ref			Ref		
Moderate	1.55	(0.99-2.41)	0.054	2.12	(1.10-4.08)	0.025
Low	1.04	(0.66-1.64)	0.874	1.16	(0.61-2.21)	0.647
Job future ambiguity						
(Low)	Ref			Ref		
Moderate	2.66	(1.53-4.62)	0.001	1.90	(0.91-3.94)	0.086
High	2.38	(1.37-4.17)	0.002	1.32	(0.63-2.75)	0.452
Variance in workload						
(Low)	Ref			Ref		
Moderate	1.16	(0.71-1.88)	0.561	1.37	(0.67-2.82)	0.389
High	1.14	(0.73-1.78)	0.564	1.41	(0.70-2.83)	0.337
Social Support from Supervisor						
(High)	Ref			Ref		
Moderate	1.80	(1.13-2.87)	0.013	0.64	(0.30-1.40)	0.263
Low	1.50	(0.94-2.40)	0.091	0.55	(0.26-1.15)	0.113
Social Support from Coworker						
(High)	Ref			Ref		
Moderate	2.80	(1.70-4.61)	<0.001	2.19	(0.98-4.92)	0.057
Low	2.45	(1.53-3.91)	<0.001	2.59	(1.25-5.39)	0.011

† , adjusted for all listed variables. Abbreviations: IA, internet addiction; CI, confidence interval; and OR, odds ratio.

others in daily life[34] and shyness with strangers positively correlated with smartphone addiction in a previous study[33]. Accordingly, people with an irritable temperament may look up strangers on the internet without meeting in person to be more familiar with strangers. Anxious temperament is associated with a number of traits, including alertness, worry, irritability, nervousness, gastrointestinal symptoms, and anxious sleep[35,36]. In addition, it is considered as a high risk factor for depressive symptoms[37], robust predictor of anxiety and depressive disorders[12], and strong predictor of suicide attempts[11]. Although it is not possible to establish a causal relationship between IA and depression because depression is multifactorial, a significant association was observed between these two variables[38]. Based on the abovementioned information, people with an anxious temperament tend to have depressive symptoms, which might be associated with IA.

Occupational stress and IA

A previous study identified a relationship between low job control and IA[5]. Our study revealed that moderate job control was associated with an increased risk of IA, contradicting the results of a previous study in Taiwan[5]. Our study showed that low social support from coworkers was associated with an increased risk of IA and Chen et al reported that high work social support reduced the risk of IA[4]. These results coincided with those of the previous Taiwanese study[5].

In previous research, job control was classified into low and high categories[5]. To increase the accuracy of the clarification, job control was classified into low, moderate, and high categories in the present study. Based on previous research[5], we anticipated that IA would be associated with low and moderate job control. However, no relationship between IA and low job control was observed. One of the questions concerning job control was "To what extent can you do your work ahead and take a short rest break during work hours?" However, workers with low job control might not take short breaks in Japan. Thus, an inability to take short breaks during work might prevent frequent internet access. This could reduce the possibility of IA among workers with low job control.

Adequate communication with coworkers is a source of social support that reduces emotional exhaustion[39]. A longitudinal study among software professionals living in the U.S. and Europe showed that promoting effective communication with coworkers leads to improve mental health[40]. Therefore, it is essential to promote indirect contact between coworkers, as adaptive coping strategies such as receiving social support from work can reduce the risk of behavioral addiction[5].

Importance of self-care and support at work

Our findings may help workers better manage internet use. An affective temperament should be considered and screened as a risk factor for early intervention, prevention, and treatment of IA. For example, cognitive behavior therapy is a universal IA treatment[41] and mindfulness may also be effective for workers' prevention of IA[42]. At the workplace, it may also be important to promote help-seeking behavior from coworkers. In addition, the recognition of workers' affective temperament by their coworkers might increase support at work. For example, frequent face-to-face contact in the workplace may establish an environment in which coworkers might easily request assistance.

Strengths and limitations

This study revealed relationship of IA with affective temperament and occupational stress among Japanese workers. Our findings may help workers understand the effect of affective temperament, which could improve their mental health. However, this study has some limitations. First, this survey might have been limited by selection bias, and the analysis was not generalized. The present study only included Japanese workers who completed an online survey, which might have increased

the number of internet enthusiasts who participated in our survey. Second, information bias could be present if respondents in large cities are more aware of problems associated with IA and are therefore more willing or hesitant to report such problems in surveys[3]. Third, because of the cross-sectional design of this study, we could not determine the causal relationship between affective temperament and IA. However, considering the stability of temperament, we believe it affects internet dependency. Fourth, the sample size might have been insufficient for logistic regression analysis in this study. Prior studies recorded a prevalence of IA of approximately 5%-19%, and this study was conducted during the COVID-19 pandemic. Therefore, we expected the prevalence of IA would be higher than previously reported (approximately 20%). We wanted to analyze approximately 20 independent variables for logistic regression; therefore, we aimed to enroll 200 participants with IA, and we enrolled approximately 1000 participants. However, the prevalence of IA in this study was approximately 13%, resulting in a smaller sample size. Fifth, this study may have some biases concerning the scales used to measure IA. The YDQ has been used in various studies, but to our knowledge, the validity of the Japanese version has not been confirmed. For a more accurate diagnosis of IA in adults, it might have been better to use the Compulsive Internet Use Scale, the Japanese version of which has been validated[43], instead of the YDQ. Sixth, this study was conducted during the COVID-19 pandemic, and participants' working conditions may have differed from the usual ones. Seventh, individuals who use the Internet for work might be more susceptible to IA; however, we did not consider the degree of their Internet usage at work. Future longitudinal studies should thus be conducted with a prospective study design, a larger sample, and more accurate assessment of IA to confirm or refute our findings.

This study demonstrated the relationship between IA and hyperthymic, irritable, and anxious temperaments as well as that with moderate job control and low social support from coworkers. To avoid IA, understanding the affective temperament, seeking help from coworkers, and managing job control may help Japanese workers better manage their internet use.

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Development of a New Model for Predicting the Risk of Inducing Allergic Symptoms on Oral Food Challenges in Children and a New Severity-predicting Application.

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Abstract

Background

Oral food challenge (OFC) test for food allergy has been routinely performed, but may cause serious symptoms, such as anaphylaxis. Therefore, it is important to accurately predict the risk of inducing allergic symptoms before OFC. The purpose of this study is to develop a new model for predicting the appearance of allergic symptoms, and an application for automatically calculating the risk value before OFC for egg.

Methods

We conducted a retrospective study involving subjects who underwent an OFC of egg in our hospital. We prepared a univariate model using the egg-white-specific IgE antibody titer alone as a predictive factor and a multivariable model using 6 risk factors such as age, status of regular egg ingestion before OFC, total egg white load at the time of OFC, total IgE antibody titer, egg-white-specific IgE antibody titer, and ovomucoid-specific IgE antibody titer and compared the accuracy of these models. The incidence of OFC-related Sampson grade 1 or higher allergic symptoms was established as the primary endpoint.

Results

We analyzed 389 patients aged 0 to 15 years. The results of receiver-operating characteristic (ROC) curve analysis showed that the areas under the curve (AUCs) for the multivariable and univariate models were 0.71 and 0.61, respectively; the accuracy of the former was higher ($p<0.001$).

Conclusions

The results suggest that a new prediction model may help to more accurately predict the risk of

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symptom induction on OFC.

Key Words: Egg allergy; Oral food challenge test; Specific IgE; Prediction model

Introduction

Oral food challenge (OFC) testing is useful for making a definitive diagnosis of food allergy or confirming safe intake and tolerance acquisition[1-2], but may induce allergic symptoms, including anaphylaxis[3]. Along with a recent increase in the number of patients with food allergy, OFC have been routinely performed in facilities other than allergy-specializing ones, further increasing the importance of accurate risk assessment before OFC.

Sine the establishment of the guidance for japanese guidelines for food allergy 2020[1] in Japan, attending physicians have individually performed pre-OFC risk assessment based on information, such as the type of allergen, history of immediate symptoms, specific IgE antibody titer, and status of allergen ingestion, in reference to these guidelines in each facility, and determined the timing of the OFC and total allergen load during the OFC. This method has a limitation: risk assessment varies, depending on each physician's experience. Furthermore, neither patients nor their parents know the clear risk value, and it is sometimes difficult for them to understand the grounds for establishing the OFC load or timing, raising an issue.

In this study, to overcome these limitations and facilitate clearer, simpler pre-OFC risk assessment and total allergen load setting, we established two new models for predicting the risk of inducing allergy, and clarified a higher-accuracy model by comparing them. In addition, we developed an application for automatically calculating the risk value with respect to egg white load through simple input.

Methods

Study design and study population

The subjects were 0- to 15-year-old children who underwent an OFC for eggs in the Department of Pediatrics, Osaka Metropolitan University Hospital, under a diagnosis of egg allergy between April 2011 and March 2022. We included the patients who had the history of allergic symptoms after egg ingestion or egg yolk-/egg white-/ovomucoid-specific IgE antibody-positive reactions. We retrospectively obtained the history of food allergy, diagnosis, age, sex, medical history, previous ingestion of the allergen to be investigated, specific IgE antibody titer against the causative food antigen, and OFC results from all subjects' medical records. The incidence of Sampson grade 1 or higher allergic symptoms on OFC was established as the primary endpoint.

Specific IgE test

The antigen-specific IgE antibody titer was measured using an ImmunoCAP™ (Thermo Fisher Diagnostics, Uppsala, Sweden). Analysis was performed, regarding a specific IgE antibody titer of <0.1 U_A/mL as 0 U_A/mL and that of $\geqq 100$ U_A/mL as 100 U_A/mL. Patients with an antibody titer of $\geqq$ 0.7 U_A/mL (CAP class 2) were regarded as positive.

Oral food challenge test

OFC with the open method was performed. Concerning the ingestion methods, the total allergen load was divided into three: 1/8-3/8-4/8, and food was ingested at 30-minute intervals. The total intake until symptom induction was regarded as the threshold of symptom induction. The severity of symptoms was evaluated using the Sampson score. The total load was established as follows: step 1,

one heated egg yolk; step 2, heated egg white at 2g or less; step 3, heated egg white more than 2g, less than 10g; and step 4, heated egg white 10g or more (corresponding to 36g of the egg white). However, in subjects who could eat an allergen even in part without symptoms, OFC was started from a step at an egg white volume exceeding the amount. In patients taking regular drugs, the drugs were discontinued before OFC, as prescribed in the Japanese pediatric guideline for food allergy.

Statistical analysis

Data were collected from 389 subjects who underwent an OFC for eggs in our hospital. For an OFC for egg white, we initially established a multivariable prediction model prepared based on several risk factors to predict the probability that Sampson grade 1 or higher symptoms may be induced. To confirm the usefulness of this multivariable model as a predictive model, we established a univariable model (conventional model) in which the egg-white-specific IgE antibody titer alone was set as a risk factor, and compared the accuracy. The multivariable model consisted of 6 risk factors: the age, status of regular egg ingestion before OFC, total egg white load (2 categories: $\leqq$2g and $>$2g) on OFC, total IgE antibody titer, egg-white-specific IgE antibody titer, and ovomucoid-specific IgE antibody titer, which may influence the appearance of symptoms of food allergy. Using the interaction term of the total, egg-white-specific, and ovomucoid-specific IgE antibody titers as an explanatory variable, we analyzed the influence of these predictive factors on the Sampson grade (4 categories: 0, 1, 2, and $\geqq$3) as an objective variable by ordinal logistic regression analysis. In the conventional model, the egg-white-specific IgE antibody titer, which had been used as a predictive factor for a probability curve representing the possibility of symptom induction, was used as an explanatory variable, and analysis was performed, as described for the multivariable model. Of the data used for analysis, 4 variables: the status of regular egg ingestion before OFC, total IgE antibody titer, egg-white-specific IgE antibody titer, and ovomucoid-specific IgE antibody titer, included missing values; therefore, the missing values were complemented using multiple imputation. Furthermore, 142 examinees were duplicated, and robust covariance was estimated. The presence or absence of overfitting of the multivariable model was validated using the Bootstrap method 200 times, and its absence was confirmed (calibration slope=0.822). Next, the predicted probability that the Sampson grade may be evaluated as 1 or higher was calculated based on the data from 389 examinees in both the multivariable and conventional models. We compared these two models based on the ROC curve, net reclassification improvement (NRI), and integrated discriminant improvement (IDI) by dividing the examinees into two groups (Sampson grade $\geqq$1 or $<$1) on actual challenge testing, and investigated the prediction accuracy of the multivariable model.

All statistical inferences were made with a two-sided significance level of 5% using R software version 3.5.1 (https://www.r-project.org/foundation/).

Ethics statement

The protocol of this study was approved by the medical research ethics review board of Osaka Metropolitan University (Approval No.: 2021189). Informed consent was obtained from the patients or their parents via Opt-out.

Results

Demographic and characteristics of patients

The subjects were 389 patients aged 0 to 15 years (Tables 1 and 2). The median age was 3 years. They consisted of 255 boys and 134 girls. Sixty patients had a history of anaphylaxis after egg

Table 1. Demographics of patients with egg allergy

Characteristic	Patients with egg allergy (n=389)
Age, median, y	3 (0-15)
Male sex, No. (%)	255 (65)
History, No. (%)	
Atopic dermatitis	200 (51)
Bronchial asthma	94 (24)
Allergic rhinitis	48 (12)
Anaphylactic history of hen's egg	60 (15)
Anaphylactic history of other food	31 (7)
Laboratory date, median (quartile)	
Total IgE (IU/mL)	227 (0-9119)
Specific IgE (U_A/mL)	
Egg white	12.2 (0-100)
Egg yolk	2.7 (0-69.1)
Ovomucoid	4.2 (0-100)
Status of regular egg ingestion before OFC, No. (%)	
None	146 (37)
Egg yolk	83 (21)
Egg white	118 (30)

Values are expressed as medians (range) or numbers (percentage).

Table 2. Results of OFC with egg allergy

Characteristic	Patients with egg allergy (n=389)
Total egg load at the time of OFC	
Step 1 (Egg yolk), No (%)	38 (10)
Step 2 (Egg white 2g or less), No (%)	215 (55)
Step 3 (Egg white more than 2g, less then 10 g), No (%)	65 (17)
Step 4 (Egg white 10g or more), No (%)	71 (18)
The rate of OFC positivity, No (%)	183 (47)
Sampson score	
Grade 1, No (%)	65 (36)
Grade 2, No (%)	86 (47)
Grade 3, No (%)	31 (17)
Grade 4, No (%)	1 (0)
Grade 5, No (%)	0 (0)
Symptoms	
Skin, No (%)	104 (57)
Respiratory, No (%)	52 (28)
Gastrointestinal, No (%)	84 (46)
Cardiovascular, No (%)	5 (3)
Neurological, No (%)	17 (9)

Values are expressed as numbers (percentage). OFC, oral food challenge.

ingestion. Atopic dermatitis was noted in 51% of the subjects, bronchial asthma in 24%, and allergic rhinitis in 12%. The median total, egg-white-specific, and ovomucoid-specific IgE antibody titers were 227 IU/mL, 12.2 UA/mL, and 4.2 UA/mL, respectively. There were 80 patients who did not meet the

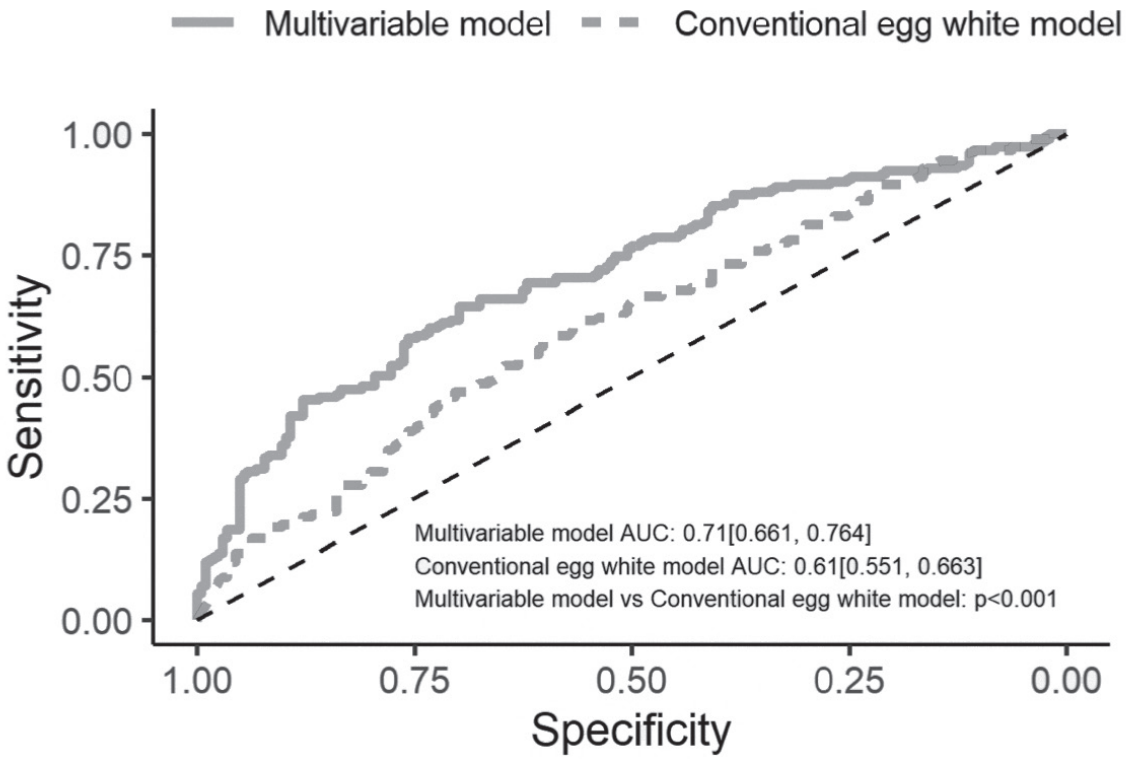

Figure 1. ROC curve of the conventional model and multivariable model for egg allergy.
ROC, receiver operating characteristic; and AUC, area under the curve.

criteria for the discontinuation of regular drugs (20%).

ROC curves of multivariable and conventional egg white model

Figure 1 shows the receiver-operating characteristic (ROC) curves for predicted probability obtained using two multivariable and conventional egg models. The area under the curve (AUC) for the multivariable model was 0.71 [0.656, 0.76], and that for the conventional model was 0.60 [0.549, 0.661]. The prediction accuracy of the multivariable model was higher than that of the conventional model ($p<0.001$).

An automatic calculation sheet of Egg OFC predicted probability

Figure 2A shows the automatic calculation sheet of predicted probability with egg OFC-positive outcomes. We adopted a new application in which the possibility that positive symptoms may appear on challenge tests at ≦2g or >2g of egg white is automatically calculated by filling in the blanks on egg allergy, such as the age, status of egg ingestion before OFC, total IgE antibody titer, egg-white-specific IgE antibody titer, and ovomucoid-specific IgE antibody titer. Figure 2B shows the possibility that allergic symptoms may appear on a challenge test at ≧2g of egg white in a subject who could ingest 1g of egg white without allergic symptoms before 2 years of age as a representative case of sheet usage. The actual application is available on the homepage https://shokokomatsu.shinyapps.io/20201220_foodchallenge_egg_binaryamount_shiny/.

Comparison of multivariable and conventional models' prediction accuracy

We verified two models' prediction accuracy with NRI and IDI (Fig. 3). There were significant inter-model differences in NRI (0.57; 95% Confidence interval (CI), 0.38-0.76; $p<0.001$) and IDI (0.09; 95% CI, 0.07-0.12; $p<0.001$).

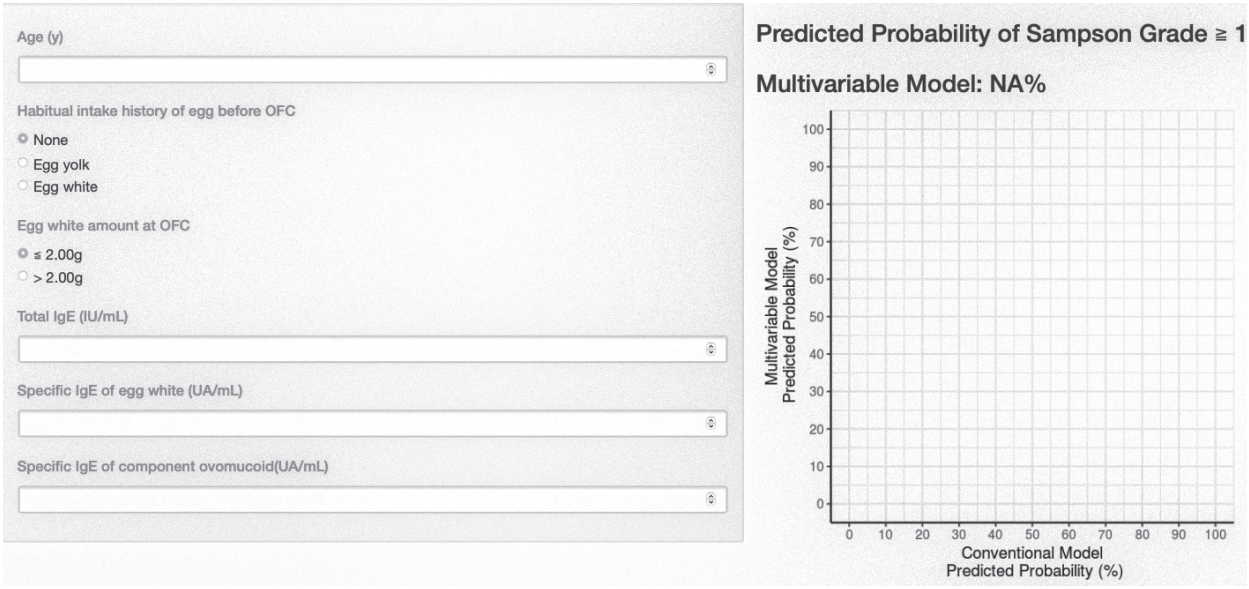

Figure 2A. Automatic calculation sheet for positive rate of oral food challenge (OFC) test for egg.
This is a sheet that automatically calculates the positive predictive rate of the egg oral challenge test. If we enter the age, habitual intake history of egg before OFC, egg white amount at OFC, Total IgE, Specific IgE of egg white, and Specific IgE of ovomucoid to the sheet, it will automatically calculate the probability of having Sampson grade 1 or higher symptoms.

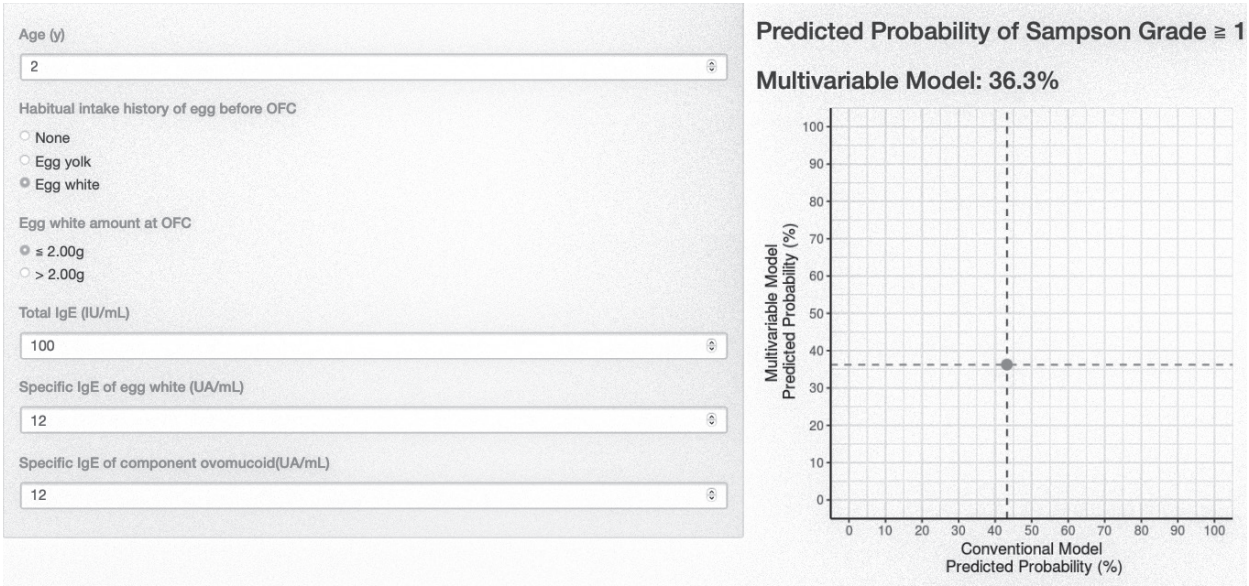

Figure 2B. How to use positive rate automatic calculation sheet.
The figure shows the possibility of the appearance of allergic-induced symptoms in a child of age 2 years who has previously been able to consume 1g of egg white without allergic symptoms, when a challenge test of 2g of egg white or more is conducted.

Discussion

In this study, we developed a new model for predicting the risk of OFC for egg allergy, as well as an automatic calculation application for digitizing predictive values using this model.

We prepared two new predictive models: a conventional model consisting of the egg-white-specific IgE antibody titer alone and a multivariable model consisting of several risk factors, such as the age,

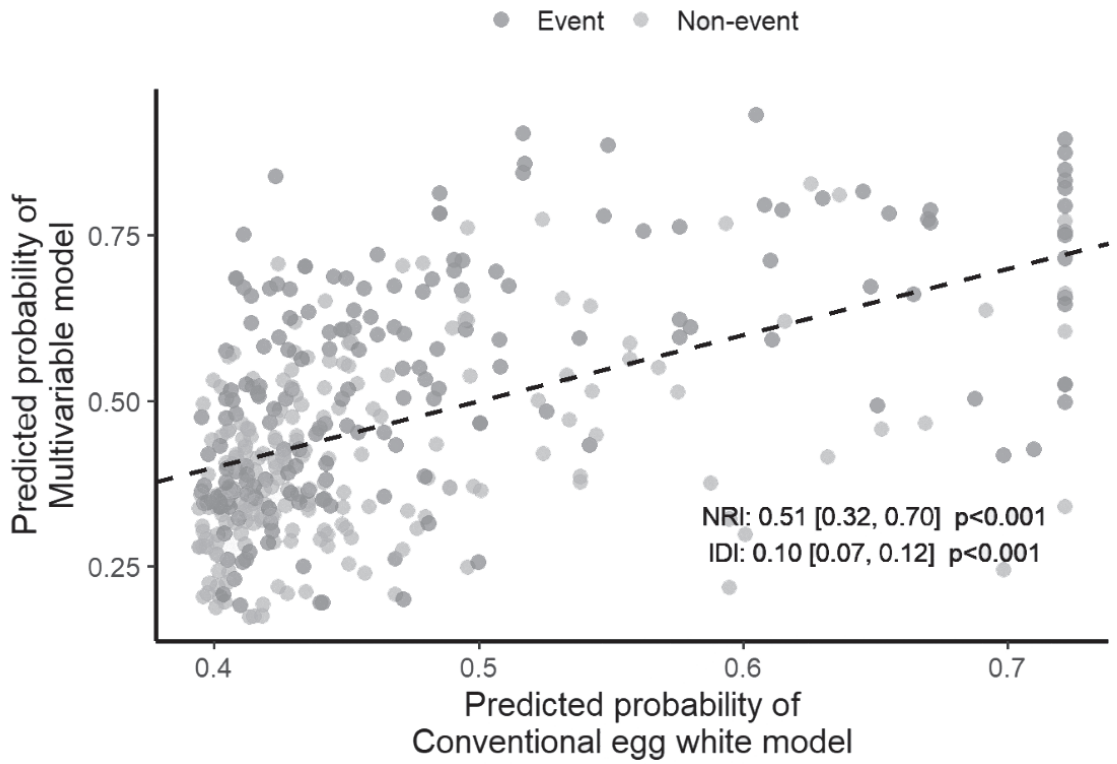

Figure 3. Predictive probabilities of the conventional model and multivariable model.
NRI, net reclassification improvement; and IDI, integrated discrimination improvement.

status of regular egg ingestion before OFC, total egg white load at the time of OFC, total IgE antibody titer, egg-white-specific IgE antibody titer, and ovomucoid-specific IgE antibody titer, and compared the prediction accuracy of the respective models. The prediction accuracy of the multivariable model consisting of several risk factors was higher. In the conventional model consisting of a risk factor that had been used in conventional probability curves[4-10], the AUC was slightly lower. Several studies predicted the risk of inducing allergic symptoms using several risk factors[11-20]. In this study, we summarized reports on egg allergy[12-14] (Table 3). Sugiura et al[12] regarded the ovomucoid-specific IgE antibody titer, age of ≧5 years, complete removal of eggs, and a total IgE antibody titer of <1000 IU/mL as risk factors, and developed a new predictive model using multivariable analysis based on these factors. They compared this model with a model prepared using the ovomucoid-specific IgE antibody titer alone, and reported the usefulness of the former consisting of several factors. According to their study, risk factors to be specially mentioned included complete removal of allergens before examination, an old age at the time of OFC, and a total IgE antibody titer of ≦1000 UA/mL. DunnGalvin et al[13] regarded the prick test, specific IgE antibody titer, value obtained by subtracting the specific IgE antibody titer from the total IgE antibody titer, clinical symptoms, and sex as risk factors, and developed a predictive model. They compared this model with a model using the specific IgE antibody titer alone as a risk factor, a model using the skin prick test (SPT) alone as a predictive factor, and a model prepared from the specific IgE antibody titer and SPT, and reported that their new model was advantageous for clinical prediction. Cianferoni et al[14] regarded the prick test, specific IgE antibody titer, history of allergic reactions other than skin reactions, and age as risk factors, developed the food challenge score, and reported its usefulness for predicting the appearance

Table 3. Previous reports of prediction models for food allergy patients.

Authors	Subject	Number of patients	Factors used for model	Outcomes	Results
Sugiura S, et al	Food allergy	198	OM-sIgE, 5 years or over, a complete avoidance of eggs, total IgE <1000 IU/mL	Identification of OFC risk factors and development of predictive models	Four factors were independently associated with severe disease: obomucoid-specific IgE class, age >5 years, complete avoidance of eggs, and total IgE <1000 IU/mL. The predictive model with those multiple factors significantly improved AUC compared to OM-sIgE alone.
DunnGalvin A, et al	Food allergy	429	Skin prick test, serum specific IgE, total IgE minus serum specific IgE, symptoms, sex, and age	Identification of OFC risk factors and development of predictive models	Prediction models based on six multiple factors: skin prick test, serum-specific IgE, total IgE-serum-specific IgE, symptoms, sex, and age were compared with models created from serum-specific IgE alone, skin prick test alone, serum-specific IgE, and skin prick test, respectively. The prediction model with multiple factors showed superiority in clinical prediction.
Cianferoni A, et al	Food allergy	983	SPT wheals, sIgE, history of a prior non-cutaneous reaction, age	Identification of OFC risk factors and development of predictive models	A Food Challenge Score (0-4) was developed which accounted for SPT wheals, sIgE, history of a prior non-cutaneous reaction, and age. A score of 0-1 had a negative predictive value for multisystem reaction to the OFC: 95% for milk, 91% for eggs, and 93% for peanuts. A score of 3-4 had a positive predictive value for anaphylaxis: 62% for milk, 92% for eggs, and 86% for peanuts.

OFC, oral food challenge; and SPT, skin pric test.

of severe reactions before OFC. These studies suggest that the severity of allergic reactions on OFC testing can be predicted from clinical data commonly available before an OFC. In this study, in our multivariable model, we regarded the age[21-22], egg-white-specific IgE antibody titer[7,23-24], ovomucoid-specific IgE antibody titer[10,25], total IgE antibody titer[26], and total load on OFC[27], which were also regarded as risk factors in other studies, as risk factors in reference to the above studies, and newly added the status of regular egg ingestion before an OFC as a risk factor to examine the usefulness of our model as a predictive model. In this study, this multivariable model was more accurate than the conventional model consisting of the specific IgE antibody titer alone, supporting the previously reported[11-20] usefulness of prediction using several risk factors for risk prediction. Furthermore, it was suggested that a new factor, the status of regular egg ingestion before OFC, improves the usefulness of pre-examination risk assessment. In addition, in this study, the development of a new severity-predicting application made it possible to automatically calculate the positive rate on challenges in individual patients; it may facilitate risk assessment in clinical practice. Concerning SPT, some studies reported it as a risk factor[28-31], whereas others indicated that the specificity of SPT reduced with children's growth/development[1], which is not limited to eggs, and that its correlation with the specific IgE antibody titer depended on age[32]. Furthermore, the results of SPT may be influenced by oral anti-allergic drug administration, differing from the specific IgE antibody titer; therefore, in this study, SPT was not added as a predictive factor.

As the limitations of this study, firstly, OFC was conducted in a single facility; if this test is performed in facilities involving children with lower- or higher-grade severity, different results may be obtained. However, our facility is an allergy-specialized institution, and if OFC is performed at a non-specialized institution, the number of patients with lower-grade severity may be larger than in our hospital; therefore, the actual risk may be slightly lower than the risk value automatically

calculated in this study. Secondly, the establishment of initial load may depend on inquiries by attending physicians at the outpatient clinic. Several attending physicians were responsible for OFC in this study, but these tests were conducted by physicians specializing in allergy at a single facility; therefore, there may have been no marked differences in allergen load. Thirdly, insufficient input items make automatic calculation impossible; therefore, if the specific IgE antibody titer is not tested on hematology, risk assessment may be impossible. However, the specific IgE antibody titer is also used in other risk prediction methods, and assessment is impossible, as described for this application.

Lastly, if the usefulness of this new application for automatic calculation obtained in this study is demonstrated in clinical practice, allergens, such as wheat/milk, against which the number of patients with allergy is large and the total number of challenge tests is great, and high-grade severity allergens, such as nuts, should also be simulated. This may be important for performing safer, more efficient OFC in the future.

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1. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866-1874.
2. Schwartz PJ, Priori SG, Napolitano C. The long-QT syndrome. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. 3rd ed. Philadelphia: W.B. Saunders; 2000. pp. 597-615.

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