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# Evaluation frameworks for technology transfer projects: Lessons from Japan's global growth of medical technologies initiatives in low- and middle-income countries

Yuta Yokobori<sup>\*</sup>, Ayumi Miyagi, Mari Nagai, Eiichi Shimizu, Tomoo Ito, Kazuki Miyazaki, Megumi Fujii, Tomoko Nishioka, Rei Haruyama, Yuriko Egami

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**Abstract:** Understanding the evaluation framework for assessing the outcomes of projects following complex technology transfer processes is limited. Therefore, we conducted a study to develop and investigate the validity of performance indicators of the technology transfer process. The performance indicators, consisting of ten indicators each for "health technology" and "health products", were developed using the Delphi method and a relationship diagram was generated. To examine validity, correlations between indicators were analyzed using a questionnaire regarding the essential factors influencing health technology and product transfer. A mutual contributory relationship between indicators related to health technology and products may exist. One of the factors promoting technology transfer was projects lasting three or more years, although no significant correlation was detected between other public support utilization and performance indicators. However, the indicators do not fully cover the technology transfer process, such as the pathway to procurement of "health products." Future research is necessary to improve performance indicators through on-site investigations.

Keywords: health technology, technology transfer, low-and middle-income countries, universal health coverage

#### Introduction

Goal 3 of the Sustainable Development Goals states that "access to quality essential healthcare services and access to safe, effective, quality, and affordable essential health products such as medicines, vaccines, and medical devices for all" are critical for achieving universal health coverage (I). Nevertheless, many low- and middleincome countries (LMICs) lack access to quality public health goods (2), resulting in negative effects on health of the population.

Similar to many other countries and organizations, the Japanese government is working to promote the international expansion of health systems, technologies, personnel, and related products to other nations, ensuring mutual benefits for both parties. As part of this effort, the Projects for Global Growth of Medical Technologies has been implemented since 2015 as a grant program by the National Center for Global Health and Medicine (NCGM), which functions as the secretariat, overseeing the management, monitoring, and evaluation of the entire project, handling approximately 30 projects annually in approximately 34 countries (*3*). However, the degree of technology transfer and its contribution to health outcomes vary.

The variability in health outcomes can attribute to the fact that health technologies and products are not always transferred in a manner appropriate for the country (4). For example, the establishment of health technologies is affected by several factors, such as needs, training content, and educational system. Furthermore, some health products may remain unused due to a discordance in product needs and a lack of public infrastructure, spare parts, consumables, or trained technicians (5), whereas other health products may not comply with local certification systems or the treatment guidelines of local governments. The improper utilization of health products can affect health outcomes (6). The equitable delivery of health products and services is becoming increasingly complex owing to pharmaceutical regulations and geographical disparities, as evidenced by the distribution of vaccines and related supplies to combat coronavirus disease 19 (7,8).

To delineate the intricate processes associated with access to and delivery of health technologies and products in LMICs, several conceptual frameworks exist, such as the Consolidated Framework for Implementation Research (9) for health technologies and health products, the pharmaceutical value chain by the United Nations (10), the modified value chain by the World Health Organization (WHO) (11), and the framework by the UN Development Programme Access and Delivery Partnership (12). In our previous study (13), we proposed seven steps for achieving equitable access to and delivery of health products based on our experience and document review (14). However, there is a limited understanding of the performance indicators for assessing the processes of health technology and health product transfer in one framework. We reviewed key lessons from the development and validation of performance indicators for projects transferring health technology to LMICs. Furthermore, it served as a case study to examine the validity of the Projects for Global Growth of Medical Technologies.

#### **Development of performance indicators**

The performance indicators for projects involving transfer of health technology and health products were developed from two perspectives: the technical aspect (hereinafter "health technology") and the deployment of health products (hereinafter "health products" in this paper) using the Delphi method (14). Specifically, we posed questions about essential factors influencing health technology and product transfer to several experts with experience in technical cooperation projects in LMICs from the NCGM using a questionnaire developed in this research (Supplemental Table S1, https://www.ghmopen. com/site/supplementaldata.html?ID=100). The responses were categorized into performance indicators under expert consensus and organized as part of the health technology and product transfer process. Subsequently, the drafted performance indicators were reviewed by experts and finalized. A diagram to describe the relationship (hereinafter "relationship diagram") between the indicators was also developed.

Furthermore, in order to examine validity of the performance indicators, the correlations between indicators according to the "relationship diagram" were analyzed using actual health technology transfer projects. For this purpose, a questionnaire was developed to evaluate the Projects for Global Growth of Medical Technologies that support human resource development (HRD) by providing training for key staff using targeted health technology and health products in recipient countries (Supplemental Table S1, https://www.ghmopen. com/site/supplementaldata.html?ID=100). We obtained responses from project representatives between 2017 and 2022 using an online tool, viz. Microsoft Forms. Projects conducted over multiple years on the same theme were treated as a single project for evaluation purposes. Additionally, we collected background information on the target region, target technology/products, project

duration, and utilization of other public support.

Thereafter, the percentage of projects relevant to each performance indicator were calculated among all projects for "health technology" indicators and among the projects handling health products for "health product" indicators. Responses marked as "unknown" for each performance indicator was considered as not having met the indicator at the time of evaluation. Correlations were statistically assessed using the chi-squared test. The nature of the performance indicators was investigated by examining the factors influencing them. Collected data were analyzed using Microsoft Excel 2021.

This study was approved by the ethics review board of the NCGM (NCGM-S-004703-00).

# Structure of Performance indicators to evaluate projects of technology transfer to LMICs

Ten performance indicators were identified for "health technology", including 7 process indicators and 3 outcome indicators. Similarly, 10 performance indicators were identified for "health products", which included 6 process indicators and 4 outcome indicators. The outcome indicators were "increased patient access", "improved health impact", "sales increase", and "spread to other countries". These indicators are shown in Table 1, while the "relationship diagram" is depicted in Figure 1.

#### Evaluation of the Projects for Global Growth of Medical Technologies for the validation of performance indicators

#### Characteristics of the projects

Eighty-four Projects for Global Growth of Medical Technologies were identified between 2017 and 2022 and representatives of 72 (85%) projects responded to the survey for validation of performance indicators. Figure 2 shows the distribution of the projects' target countries. Asia had the highest percentage of projects at 88%, followed by Africa at 10%. Within Asia, Vietnam had the highest number of projects, followed by Myanmar and Mongolia, respectively. Table 2 illustrates characteristics of the projects. In terms of clinical departments, projects dealing with surgical technology were the most numerous, followed by those pertaining to emergency care and infectious diseases. In the paramedical sector, projects focusing on diagnostic testing technology were the most common, followed by educational support and rehabilitation projects. Fifty-one (70.8%) projects entailed the handling of health products; the breakdown is shown in Supplemental Table S2 (https://www. ghmopen.com/site/supplementaldata.html?ID=100). Endoscopy-related projects were the most common, followed by ultrasound, pharmaceutical, and diagnostic equipment projects. Thirty-nine projects (54.2%) lasted 1-2 years, whereas 33 projects (45.8%) lasted 3 years

#### Table 1. Performance indicators of projects for technology transfer to LMICs

#### Health technology

No.		Indicators	Description
1	Process	Improved knowledge	Improved understanding of health technology and development of personnel capable of diagnosing and treating patients using health technology
2		Dissemination of knowledge	Dissemination of requisite knowledge and skills for use of health technology by trained health personnel to others
3		Continuous use of training materials	Continued local use of already developed training materials for health technology
4		Guideline	Reflection of health technology in guidelines of government or academic society
5		Education program	Incorporation of health technology into the educational programs for health professionals
6		Professional organizations	Establishment of health professional systems and organizations related to the health technology
7		Human resource development (HRD) using a local budget	Use of local government budgets to train health personnel in the use of the health technology
8	Outcome	Increased patients	Increased in number of patients who received diagnosis and treatment related to the
9		Health impacts	health technology
10		Spread to other countries (health technology)	Realization of health impact created by the health technology (decreased mortality or morbidity, improved QOL, <i>etc.</i> ) Implementation of activities that disseminated health technology beyond the target country (contribution to international guidelines, dissemination to other countries, input in international conferences, <i>etc.</i> )

Heal	lealth products					
No.		Indicators	Description			
11	Process	Regulatory authorization	Notified body of the target country granted approval/license for the health product			
12		Health insurance coverage	Health insurance started to cover health product			
13		Listing of health products	National medical device list started to cover health product			
14		Local distributor	Local distributer was established/identified for the health product			
15		Procurement by local budget	Health product was procured by a local budget in target country			
16		Continuous use of health product	Health product was continuously used in target country			
17	Outcome	Increased patients	The number of patients who received diagnosis and treatment related to the health technology increased			
18		Health impact	The health technology created health impacts (decreased mortality or morbidity, improved QOL, etc.)			
19		Sales increase	The health product was continuously marketed in target country			
20		Spread to other countries (health product)	The health product was procured in areas other than target country			

QOL: quality of life, LMIC: low- and middle-income countries.



Figure 1. Relationship of performance indicators.

or more. Twenty-five projects answered affirmatively regarding utilization of other public support, accounting for 34.7% of the total.

#### Project evaluation by the performance indicators

The results of the evaluation of the Project for Global Growth of Medical Technologies are presented in Table 3. For "health technology", projects pertaining to the dissemination of knowledge/skills and continuous use of training materials accounted for 45 (62.5%) and 29 (40.3%) of 72 projects, respectively. HRD system was defined by the presence of at least one of the following performance indicators: incorporation into educational



Figure 2. Distribution of target countries of the Projects for Global Growth of Medical Technologies between 2017-2021.

programs, establishment of academic societies/ professional organizations, and incorporation into guidelines, and 30 projects met this indicator (41.7%). By the end of the project, the recipient country's government had independently organized training in 34 projects (47.2%). Outcome indicators, such as increased number of patients and manifestation of health impact, were reported in 27 (37.5%) and 20 (27.8

 
 Table 2. Characteristics of the Projects for Global Growth of Medical Technologies between 2017-2021

Characteristics	Projects
Duration, Cases (%)	
One year	26 (36.1%)
Two years	13 (18.1%)
More than three years	33 (45.8%)
Other public supports	
Yes	25 (34.7%)
No	47 (65.3%)
Themes: Clinical Department	
Surgery	8
Emergency	6
Infectious disease	5
NCDs, mental and advanced medicine	4
Health check-up	4
Cancer	3
MCH	3
General medicine	1
Themes: Paramedical sector	
Diagnostics	8
Education	5
Rehabilitation	5
Radiology	5
Medical Equipment engineering	4
Dialysis	4
Blood transfusion	3
Endoscopy	2
Pharmaceutical management	2

Table 3.	Results o	f evaluation	for the	Projects	for Global	Growth	of Medical	Technologies

Results	Projects	
Health technology (72 projects in total)		
① Improved understanding of health technology	72 (100%)	
2 Dissemination of knowledge/skills	45 (62.5%)	
③ Continuous use of training materials	29 (40.3%)	
(4) Incorporation into education programs	24 (33.3%)	
(5) Establishment of academic society/professional organization	5 (6.9%)	
6 Incorporation into guideline	13 (18.1%)	
⑦ Human resource development (HRD) using the local budget	34 (47.2%)	
⑧ Increased number of patients	27 (37.5%)	
(9) Manifestation of health impact	20 (27.8%)	
0 Activities that spread the health technology beyond the target country	24 (33.3%)	
Health product (total: 51)		
(1) Acquisition of a license of the health product	5 (9.6%)	
2 Acquisition of health insurance coverage of the health product	3 (5.9%)	
(13) Inclusion of the health product in the list of medical devices	2 (3.9%)	
(1) Selection of local distributors for the health product	7 (13.5%)	
(5) Procurement of the health product by local budget	23 (42.3%)	
(f) Continuous use of the health product	32 (61.5%)	
(7) Increased sales of the health product	8 (15.4%)	
<sup>(B)</sup> Procurement of the health product in other countries.	6 (11.5%)	

%) projects, respectively. Additionally, among the 51 projects dealing with health products, 23 (42.3%) led to procurement, and 32 (61.5%) reported continuous usage. Eight projects (15.4%) increased sales of health products. However, questions regarding sales improvements were challenging to answer, leading to difficulties in evaluation.

#### Correlations between performance indicators

Figure 1 shows correlations between the indicators. Table 4A shows the relationship between the HRD system and the outcomes of health technology and health product transfer. The HRD system was statistically associated with outcome indicators, such as HRD by local budget, increased number of patients, and health impact. Similarly, regarding "health product" indicators, Table 4B shows the relationship between procurement by local budgets and outcomes of heath technology and health product transfer. Procurement based on local budgets was significantly associated with continuous use and an increase in the number of patients. Additionally, the mutual relationship between indicators of "health technology" and "health products" was analyzed (Table 4C). Among the 24 projects that established an HRD system, 15 (51.7%) and 18 (75%) led to the procurement of health products and their continuous usage, respectively. These figures are statistically greater for procurement in projects with HRD systems compared with projects that did not establish HRD systems.

Table 4A. Relationship between human resource development system and the outcome of technology transfer (number of projects)

HRD System*	Local	Local budget use		sed patients	Positive health impact		
Established (30)	20	66.7%	16	53.3%	13	43.3%	
No Established (42) <i>p</i> value**	14	33.3% < 0.05	11	26.2% < 0.05	8	19.0% < 0.05	

\*HRD system was characterized by the inclusion of at least one of the following: Incorporation into education programs, establishment of academic society/professional organization, or incorporation into guidelines. \*\*p value is calculated by chi-square test.

### Table 4B. Relationship between procurement using local budgets and the outcome of technology transfer among projects that included health products (number of projects)

Procurement*	Conti	nuous use	Increas	sed patients	Positive health impact		
Procurement (23)	18	78.2%	15	65.%	10	43.5%	
Non-procurement (28)	14	50%	10	35.75	8	28.6%	
<i>p</i> value**		< 0.05		< 0.05		0.268	

\*Procurement: Procurement of health product using the local budget. \*\*p value is calculated using chi-squared test.

### Table 4C. Relationship between "health technology" and "health product" in the 51 projects that included medical products (number of projects)

HRD system*	Pro	curement	Continuous use		
Established (24)	15	51.7%	18	75.0%	
Not established (27)	8	36.4%	14	57.2%	
<i>p</i> value**		< 0.05		0.088	

\*HRD system was characterized by the inclusion of at least one of the following: Incorporation into education programs, establishment of academic society/professional organization, or incorporation into guidelines. \*\*p value calculated using chi-squared test.

#### Table 4D. Relationship between performance indicators and characteristics (number of projects)

	All	projects (72)			Proje	ects which tr	ts which treated medical devises (51)			
	ystem (30)	Local budget use (34)			Procure	Procurement (23)		Continuous use (32)		
Duration of project	ts				Duration of projec	ets				
1-2 years (39)	12	30.1%	14	35.9%	1-2 years (22)	7	31.8%	10	45.5%	
$\geq$ 3 years (33)	18	54.5%	20	60.1%	$\geq$ 3 years (29)	16	55.1%	22	75.9%	
<i>p</i> value*		< 0.05		< 0.05			0.10		< 0.05	
Utilization of other	r public supp	ports								
Yes (25)	15	60.0%	6	24.0%	Yes (18)	7	38.9%	14	77.8%	
No (47)	25	53.2%	7	14.9%	No (33)	16	48.5%	18	54.5%	
<i>p</i> value*		0.58		0.34	~ /		0.51		0.10	

\*p value calculated using chi-squared test.

#### Factors influencing performance indicators

Table 4D summarizes analysis of the relationship between project characteristics and their outcomes. When comparing projects lasting to 1-2 years with those lasting 3 years or more, the latter exhibited a tendency towards higher performance indicators in terms of incorporation into the education system or guidelines and procurement/ continuous usage, with statistically significant differences in other areas apart from procurement. However, no statistically significant differences were evident in the utilization of other types of public support for any performance indicator.

# Interpretation of the evaluation for the indicators' validation

In this study, the performance indicators for projects transferring health technology and health product to LMICs were developed from the dual-perspective of "health technology" and "health products". Based on evaluation of an actual project, the association between the performance indicators was statistically proved using the "relationship diagram". We confirmed the validity of the developed performance indicators to describe processes of health technology and health product transfer. With reference to the "relationship diagram" representing the steps from the introduction to the institutionalization of "health technology" and "health products", each project was evaluated according to its nature and stage of development. Furthermore, analysis of performance indicators of "health technology" and "health products" revealed mutual relationships between them. The results suggest that the integration of "health technology" into the local healthcare system is crucial for procurement and establishment of "health products" for further business development. These indicators were useful in visualizing outcomes of the complex process of technology transfer, laying groundwork for necessary interventions.

Moreover, these performance indicators were useful for investigating the factors contributing to each process of health technology and health product transfer. The results of the evaluation of the Projects for Global Growth of Medical Technologies over the past five years revealed that the duration of the project influenced performance indicators of both "health technology" and "health products". Specifically, projects lasting three or more years exhibited significantly higher performance indicators, suggesting that approximately three years may be required to achieve sufficient results. The transfer of new technology requires building relationships with local stakeholders and integrating them into the local healthcare system, which is a timeconsuming process. This may explain the results of the present study. However, there was no significant correlation between utilization of other public support

systems and any performance indicator. Although we hypothesized that the effective utilization of multiple public support systems could yield better outcomes, this was not demonstrated in this study's analysis. However, the factors affecting the complicated process of health technology and health product transfer can be analyzed in greater detail using this framework.

#### Limitations

This study has several limitations. First, data collection on performance indicators solely through surveys of project implementers may be insufficient, and some indicators may require in-depth, on-site information gathering. For example, evaluating indicators such as the health impact after the introduction of "health technology" or "health products" is time-consuming. Therefore, it is necessary to include field visit surveys with local users of health technology and health products to consider the feasibility of data collection methods and examine the validity of performance indicators. Additionally, when respondents answered "unknown" to a question in the questionnaire, we classified it as "no achievement". However, there were many such responses (11 procurement projects and 26 guidelinecreating projects). Therefore, local surveys or in-depth questionnaires are necessary to investigate projects with "unknown" responses. Furthermore, although we examined the factors influencing performance indicators, we could only conduct simple analyses using chi-squared tests owing to an insufficient number of projects, and analyses adjusting for confounding factors could not be performed. In the future, we endeavor to increase the number of projects and further investigate the various promoting and hindering factors.

#### Conclusion

We developed performance indicators for projects transferring health technology to LMICs. Based on actual project evaluations, the validity of these indicators was satisfactory. From the perspective of the complex process of technology transfer, comprehensive evaluations tailored to the nature and stage of the projects can be conducted. However, it was difficult to adequately evaluate some indicators by simply posing questions to project implementers. Therefore, in the future, we aim to further examine validity of performance indicators and explore factors that facilitate or hinder further development of projects, potentially combining them with local investigations.

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# A scoping review on mindfulness-based interventions for families of patients with advanced cancer

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**Abstract:** We aimed to conduct a scoping review to investigate mindfulness-based interventions targeting the families of patients with advanced cancer to elucidate the characteristics of the target population, program content, and evaluation methods. The review followed the Joanna Briggs Institute guidelines, and relevant studies were identified through searches in the PubMed, CINAHL, and Cochrane databases. A total of 13 studies were included, with only one focusing solely on family members, while the rest involved both family members and patients. Among the 13 studies, 4 were randomized controlled trials (RCTs), and 10 were pilot studies. The sample sizes varied, with seven studies involving single-group designs, four using two-group designs, one with a three-group design, and one study where no information on group size was provided. The framework and content of the programs were adapted from existing mindfulness-based stress reduction techniques to suit the target context and were evaluated using multiple measures, including assessments of anxiety and depression. Most studies should address the needs and challenges faced by the families of patients with advanced cancer, refining program content and evaluation methods from the perspective of nurses.

Keywords: family nursing, caregiver, mental health, intervention program, meditation

#### Introduction

The 5-year relative survival rate for all cancers has been improving annually, with approximately 70% of patients now reaching the fifth year after diagnosis (1). Although cancer is categorized as a chronic disease, advanced cases often follow a challenging course due to late detection, limited treatment options, and rapid progression. Many patients with advanced cancer undergo multidisciplinary treatment, including surgery, chemotherapy, and radiation therapy, tailored to their condition. Patients endure prolonged illness, while their families, who provide support, also experience significant strain.

Family members of patients with advanced cancer are forced to witness their loved one's suffering and the harshness of life. They sometimes endure more unbearable emotions than the patient, and referring to them as the "second" patient is not an exaggeration. From the moment of diagnosis, families take on multifaceted roles and must often restrict their social lives (2,3). Maintaining mental health becomes challenging (2), and they are sometimes required to make sacrifices in terms of their own well-being and finances (4,5). These compounded burdens affect family members' self-efficacy, quality of life (QOL), and contribute to increased rates of anxiety and depression (6,7). Approximately one-quarter of families of patients with advanced lung cancer experience depressive symptoms (8). In some cases, the anxiety experienced by family members surpasses that of the patients, depending on the nature of the disease (9).

Intervention studies using techniques, such as cognitive behavioral therapy, psychoeducation, and supportive interventions, are being conducted to reduce the burden on families of patients with advanced cancer. These studies have shown positive effects in improving the QOL of family members while also reducing levels of depression, anxiety, and caregiving strain (10-13). In recent years, mindfulness-based interventions (MBIs) have gained considerable attention. Mindfulness involves the intentional awareness of one's physical and mental processes, functioning both as a skill and a practice. The cultivation of mindfulness enhances the ability to remain present, and those who can sustain mindfulness amidst life's challenges have been

suggested to experience less suffering (14). The most widely recognized program is mindfulness-based stress reduction (MBSR), developed by Kabat-Zinn (15). This program, which typically spans 8 weeks, includes mindfulness meditation, body scanning, yoga, group discussions, and retreats. Recently, various programs have emerged, tailored to specific conditions, stages of illness, and symptoms. One such program is mindfulness-based cognitive therapy, which integrates cognitive therapy with mindfulness practices (16).

MBIs have been shown to be effective in managing mental health conditions, such as depression, anxiety disorders, and chronic pain. They also have a positive impact on stress, anxiety, fatigue, and post-traumatic growth in patients with cancer (16, 17). Additionally, MBIs have been associated with a decrease in depressive symptoms, a reduction in caregiving burden, and an improvement in QOL among the families of patients with cancer (18). Some evidence even suggests that MBIs may improve overall mood within these families (10). Furthermore, improvements in mindfulness can have a ripple effect, reducing stress within the family unit (19). This allows individuals to continue applying the self-care skills they learned through MBIs even after the program has ended. MBIs may be particularly beneficial for families of patients with advanced cancer, as these caregivers are often overwhelmed by their responsibilities and may neglect their own mental health. However, research on MBIs for families of patients with advanced cancer in Japan has been limited, focusing mainly on the experiences and needs of family members, with few reports on MBI.

To gain a deeper understanding of the potential benefits of MBIs for these families and to guide future interventions in Japan, conducting a comprehensive review of prior international studies is important. This should include an overview of their scope and content, the identification of research gaps, and scoping reviews of intervention methods and outcome measures. In this study, we aimed to conduct a scoping review of MBIs for family members of patients with advanced cancer overseas. Our goal was to clarify the intervention methods and outcome indicators to gain insights for future MBI research and practice.

#### Research methods and literature review strategy

Tal	ble	1.	Study	se	lection	criteria	
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In this study, a family includes not only blood relatives, such as parents, siblings, or spouses (in the case of marriage), but also caregivers whom the patient recognizes as being close to them. MBI refers to clinical interventions that incorporate mindfulness meditation programs.

We conducted a scoping review (20) aimed at rapidly outlining the scope and content of a specific research area. It involved an extensive search of key concepts, information sources, and types of available papers and evidence, with findings reported based on the Joanna Briggs Institute's manual for evidence synthesis (21). The criteria for selecting studies are listed in Table 1: i) population: family members of adult patients with advanced cancer (stage III or IV) undergoing chemotherapy or radiotherapy; *ii*) concept: studies that implemented clinical interventions using mindfulness meditation programs; and iii) context: studies conducted in any country and published in English, with no restrictions on the year of publication. Reviews, conference proceedings, commentaries, and studies describing only protocols were excluded.

We used the PubMed, CINAHL, and Cochrane databases to conduct the search on September 4, 2024. The search included all literature up to the year of the search, using the following search terms: "mindfulness" AND "(cancer) OR (neoplasms)" AND "(family) OR (carer) OR (caregiver) OR (partner) OR (partners) OR (partnered) OR (partnering)".

Two independent researchers screened the literature. In the first screening, titles and abstracts were reviewed against the selection criteria. In the second screening, full texts were thoroughly read. Any disagreements between the researchers were discussed, and a final decision was made regarding the inclusion of each study.

#### Key findings based on the scoping review

#### Summary of the included studies

A flowchart for selecting literature was created based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines (Figure 1). The search yielded 400 articles: 146 from Cochrane, 134 from Pubmed, and 120 from CINAHL. After applying the selection criteria and excluding

Items	Selection criteria			
Population	• Family members of adult patients with advanced cancer undergoing treatment with chemotherapy or radiotherapy, including stage III or IV.			
Concept	<ul> <li>Studies in which clinical interventions using programs incorporating mindfulness meditation are being conducted.</li> <li>Review articles, conference abstracts, conference proceedings, or commentaries, and protocol studies were excluded.</li> </ul>			
Context	• Studies from all countries written in English were included regardless of the date of publishing.			



Figure 1. PRISMA flowchart of study selection.

120 duplicates, a total of 280 articles remained. The primary screening involved reviewing the titles and abstracts, leading to the exclusion of 256 articles from further analysis. During the secondary screening, 24 full-text articles were reviewed, and 13 were finally selected. Table 2 presents an overview of the 13 selected studies. All 13 studies were published in the 2000s, with the earliest published in 2012. The most common publication year was 2020, with five studies published that year; in other years, one or two studies were published annually. The studies surveyed were primarily from the USA (n = 12) and the Netherlands (n = 1). Among the 13 studies, four were randomized controlled trials (RCTs) and 10 were described as pilot studies.

The sample sizes varied, with seven studies involving single-group designs, four using two-group designs, one with a three-group design, and one study where no information on group size was provided.

#### Outline of the participants

Of the 13 studies, one involved only family members, while the remaining 12 studies included both patients and family members. Of these, three provided programs specifically designed for patient-family member pairs. The terminology used to describe family members varied considerably across the literature. The most common term was "family caregiver" (used in four studies), followed by "partner" and "informal caregiver" (three studies each), and "family member", "spouse", and "partner" (one study each). Six studies referred to "multiple cancers", which included both solid tumors and hematological cancers. Three studies mentioned "nonsmall cell lung cancer", two addressed "small cell and non-small cell lung cancer", one focused on "malignant glioma or brain metastasis", and one referred to "head and neck cancer". In terms of cancer progression, eight studies specified the stage of cancer, whereas five did not. The cancer stages varied, with some studies including all stages from I to IV and others being limited to stage IV. Certain studies also focused on patients who had completed or were undergoing treatment (22), were undergoing curative or palliative chemotherapy (23), had incurable cancer (24), were undergoing treatment with a prognosis of 12 months or less (25), and were receiving chemotherapy for progressive disease (26).

#### Characteristics of the interventions

The intervention methods, content of the MBI programs, and outcome measures for each study are listed in Table 3.

Regarding the intervention methods, the most common duration was 8weeks, as reported in five studies, followed by 6weeks in four studies, 4weeks in three studies, and 2weeks in one study. For the duration of each session, 120 minutes was the most common (in four studies), followed by 60 minutes (in three studies). Other session lengths included 150 minutes,

Table 2.	. Summary of t	he document					
No. (Ref.)	Author (Year of Publication) Country	Title	Purpose	Research Design	Number of Participants (Number Analyzed)	Type of Cancer (Supplemental) / Stage	Family Notation
1 (30)	Lengacher et al. (2012) USA	A pilot study evaluating the effect of mindfulness-based stress reduction on psychological status, physical status, salivary cortisol, and interleukin-6 among advanced- stage cancer patients and their caregivers	To determine whether the Mindfulness-Based Stress Reduction Program for Cancer (MBSR-C) improves psychological and physical symptoms, quality of life, and stress in patients with advanced cancer and their caregivers.	one-group, quasi- experimental, pre-post test design	patient: 26 (23) family: 26 (24)	breast cancer, colon cancer, lung cancer, prostate cancer (during radiation or chemotherapy treatment) / Stage III or IV	family- caregiver
2 (22)	van den Hurk <i>et al.</i> (2015) Netherlands	Mindfulness-Based Stress Reduction for lung cancer patients and their partners: Results of a mixed methods pilot study	To determine whether MBSR is a feasible intervention for lung cancer patients and their partners, and whether it is effective in reducing psychological distress.	mixed methods pilot study	patient: 19 (13) family: 16 (11)	small cell lung cancer, non-small cell lung cancer (treatment completed or in progress) / No description	partner
3 (33)	Milbury . <i>et al.</i> (2017) USA	Pilot Testing of a Brief Couple-Based Mind-Body Intervention for Patients With Metastatic Non-Small Cell Lung Cancer and Their Partners	To examine the acceptability and effectiveness of the intervention for patients with metastatic lung cancer and their spouses undergoing treatment.	single-arm trial	patient: 7 (6) family: 7 (6)	non-small cell LC (under active treatment) / Stage IV	partner
4 (32)	Winger <i>et al.</i> (2018) USA	Coping Skills Practice and Symptom Change: A Secondary Analysis of a Pilot Telephone Symptom Management Intervention for Lung Cancer Patients and their Family Caregivers	To examine the relationship between the practice of coping skills and changes in symptoms in telephone symptom management (TSM) interventions conducted simultaneously with lung cancer patients and their caregivers.	randomized pilot trial	patient: 51 (51) family: 51 (51)	small cell lung cancer, non-small cell lung cancer (more than 3 weeks have passed since diagnosis, and at the time of recruitment, specific symptoms are moderate or more severe) / Stage I to IV	family- caregiver
5 (31)	Kubo <i>et al.</i> (2018) USA	A Pilot Mobile-based Mindfulness Intervention for Cancer Patients and their Informal Caregivers	To conduct a pilot feasibility study of an app/ online-based mindfulness program within an integrated healthcare delivery system for cancer patients and their overburdened caregivers.	single-arm pilot study	patient: 28 (19) family: 14 (9)	breast cancer, digestive organ cancer, blood cancer, lung cancer (chemotherapy scheduled within at least 2 months after diagnosis of cancer) / Stage II to IV	informal- caregiver
6 (23)	Kubo <i>et al.</i> (2019) USA	A Randomized Controlled Trial of mHealth Mindfulness Intervention for Cancer Patients and Informal Cancer Caregivers: A Feasibility Study Within an Integrated Health Care Delivery System	Based on the results of the pilot study, we will examine the feasibility and effectiveness of an mHealth mindfulness program intervention for cancer patients and their caregivers.	two-arm RCT	patient: 97 (72) family: 31 (26)	breast cancer, blood cancer, digestive organ cancer (under curative or palliative chemotherapy) / No description	informal- caregiver
7 (24)	Cottingham et al. (2019) USA	Addressing personal barriers to advance care planning: Qualitative investigation of a mindfulness-based intervention for adults with cancer and their family caregivers	To examine the impact of a new mindfulness intervention, Mindfully Optimizing Delivery of End-of-Life (MODEL) Care, on the life experiences and ACP of patients with advanced cancer and their caregivers.	No description	patient: 13 (12) family: 13 (12)	solid malignant tumors (incurable) such as metastatic melanoma, lung cancer, sarcoma, and pancreatic cancer / Stage IIIb or IIIc, IV	caregiver

(11)

Table 2.	. Summary of t	he document (continued)					
No. (Ref.)	Author (Year of Publication) Country	Title	Purpose	Research Design	Number of Participants (Number Analyzed)	Type of Cancer (Supplemental) / Stage	Family Notation
8 (27)	McDonnell et al. (2020) USA	A Prospective Pilot Study Evaluating Feasibility and Preliminary Effects of Breathe Easier: A Mindfulness-based Intervention for Survivors of Lung Cancer and Their Family Members (Dyads)	To evaluate the feasibility and preliminary effects of an intervention called Breathe Easier, which is based on evidence-based MBSR and MBCR programs, for NSCLC survivors (stages I-IIIa) and their families.	1-group pre- post design	patient: 26 (26) family: 23 (23)	non-small cell lung cancer (after first- line treatment) / Stage I to IIIa	family- member
9 (34)	Kubo <i>et al.</i> (2020) USA	Pilot pragmatic randomized trial of mHealth mindfulness-based intervention for advanced cancer patients and their informal caregivers	To conduct a feasibility study and evaluate patient preferences for two types of MBI provision, by conducting a large-scale RCT of a technology- based MBI program for patients with advanced cancer and their caregivers in a healthcare delivery system.	two-arm pilot cluster RCT	patient: 103 (80) family: 39 (33)	metastatic solid tumors such as breast cancer, gastrointestinal cancer, lung cancer, and urological cancet, or hematological cancer / No description	informal- caregiver
10 (28)	Milbury <i>et al.</i> (2020) USA	Online Couple-Based Meditation Intervention for Patients With Primary or Metastatic Brain Tumors and Their Partners: Results of a Pilot Randomized Controlled Trial	To examine the feasibility and preliminary efficacy of a Couple-Based Meditation (CBM) program for patients with primary and metastatic brain tumors and their partners, with the goal of improving symptoms and health status.	two-arm pilot trial	patient: 35 (22) family: 35 (22)	malignant glioma or solid malignant tumor that has metastasized to the brain (currently being treated) /No description	partner
11 (29)	Milbury <i>et al.</i> (2020) USA	A Mindfulness-Based Intervention as a Supportive Care Strategy for Patients with Metastatic Non-Small Cell Lung Cancer and Their Spouses: Results of a Three-Arm Pilot Randomized Controlled Trial	To test the efficacy of couple-based meditation (CBM) for patients with metastatic lung cancer and their spouses, compared to supportive expression (SE) and usual care (UC) groups, targeting psychological and spiritual distress.	three-arm RCT	patient: 75 (48) family: 75 (48)	non-small cell lung cancer (during radiation or chemotherapy) / Stage IV	spouse
12 (25)	Johns <i>et al.</i> (2020) USA	Mindfulness Training Supports Quality of Life and Advance Care Planning in Adults With Metastatic Cancer and Their Caregivers: Results of a Pilot Study	To develop and evaluate the feasibility and acceptability of a mindfulness-based intervention, Mindfully Optimizing Delivery of End-of-Life (MODEL) Care, for patients with advanced cancer and their family caregivers, and to evaluate preliminary effects.	single arm design	patient: 13 (13) family: 13 (13)	solid malignant tumor (under treatment, prognosis given by doctor is within 12 months) / Stage IIIb or IIIc, IV	family- caregiver
13 (26)	Chesak <i>et al.</i> (2022) USA	Outcomes of a Stress Management and Resiliency Training (SMART) Program for Family Caregivers of Individuals With Advanced Head and Neck Cancer	To investigate the feasibility, acceptability, and preliminary effects of the Stress Management and Resiliency Training (SMART) intervention for family members of head and neck cancer patients.	single-arm prospective pilot study	family: 26 (16)	head and neck cancer (advanced, undergoing chemotherapy) / No description	family- caregiver

(12)

Tab	le 3. Program contei	nt and evaluation meth	od				
No.	Program name	Additional items	Period/Minutes per session	Intervention Method	A person who guides mindfulness	Timing of evaluation	Measuring tools
-	MBSR program for cancer (MBSR-C)	nutrition discussion	6 weeks / 15- 45 min	3 face-to-face sessions and 3 CD sessions (group sessions)	a licensed clinical psychologist who was trained in MBSR	baseline (orientation)	<ul> <li>Perceived Stress Scale (PSS)</li> <li>Center for Epidemiologic Studies Depression Scale (C-ESD)</li> <li>State-Trait Anxiety Inventory (STAI)</li> <li>Memorial Symptom Assessment Scale (MSAS)</li> <li>Medical Outcomes Studies Short-Form General Health Survey (SF-36)</li> <li>cortisol, II-6</li> </ul>
						one week later (before and after the session)	≽ cortisol, II-6
						3 weeks later (before and after the session)	≽ cortisol, II-6
						6 weeks later (before and after the session)	≽ cortisol, II-6
						6 weeks later	Same as the baseline
0	MBSR	psychological education related to grief	8 weeks / 150 min	face-to-face	health professionals and qualified mindfulness trainer	baseline	<ul> <li>&gt; Self-Perceived Pressure from Informal Care (SPPIC)*</li> <li>&gt; Caregiver Reaction Assessment (CRA)*</li> <li>&gt; Hospital Anxiety and Depression Scale (HADS)</li> <li>&gt; Core Quality of Life Questionnaire for Lung Cancer (QLQ-LC13)</li> <li>&gt; Impact of Event Scale (IES)</li> <li>&gt; Penn State Worry Questionnaire (PSWQ)</li> <li>&gt; Mindful Attention Awareness Scale (MAAS)</li> </ul>
						8 weeks later	♦ Same as the baseline
						3 months after the program	✤ Same as the baseline
						within one year of the program ending	≽ interview
m	Couple-based mind- body (CBMB)	sharing of emotions between a couple	2 weeks / 60 min	no description	a master-level mind-body specialist	baseline (before the first session)	<ul> <li>Functional Assessment of Cancer Therapy-Spiritual Well-Being Scale (FACIT-SP)</li> <li>Center for Epidemiologic Studies Depression Scale (CES-D)</li> <li>Impact of Events Scale (IES)</li> <li>Pittsburgh Sleep Quality Index (PSQI)</li> </ul>

\*family only; \*\*patient only.

Tabl	le 3. Program conte	nt and evaluation meth	od (continued)				
No.	Program name	Additional items	Period/Minutes per session	Intervention Method	A person who guides mindfulness	Timing of evaluation	Measuring tools
						within one week of the program ending	➤ before the first session
4	Telephone symptom management (TSM) intervention	symptom management	4 weeks / 45- 60 min	phone-based session	licensed clinical social worker	baseline	<ul> <li>Brief Pain Inventory-Short Form</li> <li>Fatigue Symptom Inventory (FSI)</li> <li>Memorial Symptom Assessment Scale (MSAS)</li> <li>Patient Health Questionnaire (PHQ-8)</li> <li>Generalized Anxiety Disorder scale (GAD-7)</li> </ul>
						6 weeks later	▶ same as the baseline
Ś	Commercial mindfulness mobile application Headspace <sup>TM</sup>	no description	8 weeks / 10- 20 min	application	not applicable	at the time of registration	<ul> <li>NCCN Distress Thermometer</li> <li>Hospital Anxiety and Depression Scale (HADS)</li> <li>Pittsburg Sleep Quality Index (PSQI)</li> <li>PROMIS Global Health Scale</li> <li>Brief Fatigue Inventory</li> </ul>
						8 weeks later	<ul> <li>same as when it was registered.</li> <li>telephone interview</li> </ul>
Q	Commercial mindfulness mobile application Headspace <sup>TM</sup>	no description	8 weeks / 10- 20 min	application	not applicable	when consent is obtained	<ul> <li>NCCN Distress Thermometer</li> <li>Hospital Anxiety and Depression Scale (HADS)</li> <li>PROMIS Pain Intensity numeric rating scale</li> <li>PROMIS Sleep Disturbance scale</li> <li>Functional Assessment of Cancer Therapy General Scale (FACT-G)</li> <li>Brief Fatigue Inventory</li> <li>Posttraumatic Growth Inventory (PTGI)</li> <li>Five Facet Mindfulness Questionnaire–Short Form (FFMQ-SF)</li> </ul>
						8 weeks later	<ul><li>Same as when consent was obtained</li><li>telephone interview</li></ul>
7	Mindfully Optimizing Deliverv	practice mindful dialogue and listening.	6 weeks / 120 min	face-to-face	a facilitator with extensive training in	1 weeks later	> questionnaire (published in a different journal)
	of End-of-Life (MODEL) Care	ACP			mindfulness teaching and practice methods	4 weeks later	▶ the same as one week later
						within one week of the program ending	▶ interview

\*family only; \*\* patient only.

Tabl	e 3. Program conte	ent and evaluation metho	od (continued)				
No.	Program name	Additional items	Period/Minutes per session	Intervention Method	A person who guides mindfulness	Timing of evaluation	Measuring tools
∞	Breathe Easier	presentations on multiple the mes, including retreats, breathing difficulties and COPD	8 weeks+ retreat / 120 min	face-to-face	an advanced practice nurse and a board- certified psychiatrist, both of whom were mindfulness pactitioners	2 weeks later	<ul> <li>&gt; FACIT - Dyspnea 10 Item Short Form (Part 1)</li> <li>&gt; FACIT Fatigue Scale (Version 4)</li> <li>&gt; Perceived Stress Scale (PSS)</li> <li>&gt; Pittsburgh Sleep Quality Index (PSQI)</li> <li>&gt; Hospital Anxiety and Depression Scale (HADS)</li> <li>&gt; 6 Minute Walk Test</li> <li>&gt; Nic-Alert Saliva Test (Immunochromatographic assay for the quantitative determination of nicotine)</li> </ul>
						5 weeks later	$\succ$ the same as two weeks later
						8 weeks later	$\succ$ the same as two weeks later
						after the program ends	⊁ interview
6	Mobile-based Headspace and webinar-based eMindful	no description	6 weeks/ Headspace: 15 minutes a day with the app eMindful: 120 minutes online	application or online	not applicable	when consent is obtained	<ul> <li>Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal)**</li> <li>Caregiver Quality of Life Index-Cancer (CQOLC)*</li> <li>NCCN Distress Thermometer</li> <li>NCCN Distress Thermometer</li> <li>Five Facet Mindfulness Questionnaire (FFMQ-SF)</li> </ul>
						6 weeks later	$\blacktriangleright$ same as when consent was obtained
						6 weeks after the program ends	➤ same as when consent was obtained
						after the program ends	> telephone interview
10	Couple-Based Meditation (CBM)	sharing of feelings between couples, ACP	4 weeks / 60min	online	A master-level licensed phycological counselor intern	baseline	<ul> <li>&gt; MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT)</li> <li>&gt; Center for Epidemiologic Studies-Depression Scale (CES-D)</li> <li>&gt; Mindful Attention Awareness Scale (MAAS)</li> <li>&gt; Self-Compassion Scale (SCS)</li> <li>&gt; Personal Assessment of Intimacy in Relationships Inventory</li> </ul>
						6 weeks later	$\checkmark$ same as the baseline
						12 weeks later	$\blacktriangleright$ same as the baseline
*fami	ly only; **patient only						

Tabl	e 3. Program conte	nt and evaluation metho	od (continued)				
No.	Program name	Additional items	Period/Minutes per session	Intervention Method	A person who guides mindfulness	Timing of evaluation	Measuring tools
=	Couple-Based Meditation (CBM)	sharing of feelings between couples, ACP	4 weeks / 60 min	online	A master's licensed phycologist counselor intern	baseline	<ul> <li>&gt; depression symptoms with the Center for Epidemiologic Studies Depression Scale (CES-D)</li> <li>&gt; Impact of Event Scale (IES)</li> <li>&gt; Functional Assessment of Cancer Therapy-Spiritual Well- Being Scale (FACIT-SP)</li> </ul>
						1 month later	➤ same as the baseline
						3 months later	★ same as the baseline
12	Mindfully Optimizing Delivery of End-of-Life (MODEL) Care	ACP	6 weeks / 120 min	face-to-face	A certified mindfulness facilitator with extensive training in mindfulness- based teaching methods	baseline	<ul> <li>McGill Quality of Life Inventory**</li> <li>Caregiver Quality of Life Index-Cancer (CQOLC)*</li> <li>Openness to Discuss Cancer in the Nuclear Family (ODCNF)</li> <li>Mini-Mental Adjustment to Cancer Scale (Mini-MAC): Cognitive Avoidance</li> <li>Brief COPE: self-distraction, denial, behavior disengagement</li> <li>Patient Health Questionnaire (PHQ-8)</li> <li>Generalized Anxiety Disorder scale (GAD-7)</li> <li>Pittsburgh Sleep Quality Index (PSQI)</li> <li>Fatigue Symptom Inventory (FSI)</li> </ul>
						after intervention	<ul> <li>&gt;</li></ul>
						4 weeks after the program ends	▶ same as the baseline
13	The Stress Management and Resiliency Training (SMRT)	stress management and resilience training session	8 weeks / no description	f a c e - t o - f a c e explanation and online (phone confirmation)	no description	baseline	<ul> <li>Perceived Stress Scale (PSS)</li> <li>Self-Compassion Scale Short Form (SCS-SF)</li> <li>Connor-Davidson Resilience Scale (CD-RISC)</li> <li>PROMIS Short Form v1.0-Anxiety 8a</li> <li>Mindful Attention Awareness Scale (MAAS)</li> </ul>
						8 weeks later	➤ same as the baseline
*fami	ly only; **patient only.						

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(16)

15-45 minutes, and 45-60 minutes, each reported in one study, while another study noted a range of 10-20 minutes depending on the application. Program delivery methods varied, including face-to-face sessions (22,24,25,27), online formats (28,29), a combination of face-to-face and CD-based sessions (30), the use of commercial apps (23,31), telephone-delivered sessions (32), and a blend of face-to-face explanations with online components (26). In terms of program content, only one study (22) used the existing MBSR program in its original form, while most adapted MBSR to suit the target situation. These adaptations included three couple-specific programs, namely, couple-based mind-body and couple-based meditation (28,29,33), mindfully optimizing, as well as two programs focused on end-of-life care, such as the Delivery of End-of-Life (MODEL) Care (24,25). Additionally, three programs incorporated mobile-based platforms, such as Headspace<sup>™</sup> (23,31,34), while others were cancerspecific (30), telephone-based symptom management interventions (32), or focused on breathing techniques (27). Most programs were structured to include unique sessions tailored to their specific target audience, such as discussions on nutrition (30), psychoeducation on grief (22), advance care planning (24,25,28,29), stress management, and resilience training (26).

Most of the program providers, namely the facilitators, were trained and qualified in mindfulness instruction and practice; these included clinical psychologists (28-30), social workers (32), medical professionals (22), and experts in mental and physical well-being (33). Only one study explicitly mentioned a facilitator being a nurse (27).

#### Outcome measures

The assessment instruments used in the included studies were questionnaires using established scales (six studies), combined questionnaires and semi-structured interviews (four studies), and a combination of questionnaires and telephone interviews (three studies).

The measurement tools employed in the questionnaire surveys can be broadly categorized as follows: mental and psychological state measures (*e.g.*, anxiety, depression, post-traumatic stress disorder, resilience, worry, and psychological adjustment); QOL measures; mindfulness and compassion measures; physical symptom measures (*e.g.*, fatigue, tiredness, and dyspnea); and scales assessing stress, sleep, and caregiver-related factors. Non-scale assessment methods included cortisol and interleukin-6 analysis *via* saliva sampling (*30*), the NicAlert saliva test, which measures nicotine levels in saliva, and the six-minute walk test (*27*).

The most commonly used scale was the hospital anxiety and depression scale (22,23,27,31,34), used in five studies. In addition, the Center for Epidemiologic

Studies Depression Scale (28,29,30,33), which assesses depressive symptoms over the past week, and the Pittsburgh sleep quality index (25,27,31,33), which measures sleep quality, were each used in four studies. Other scales include the impact of event scale (22,29,33), which measures intrusive experiences and avoidance of event-related thoughts and images, and the perceived stress scale (26, 27, 30), which assesses how stressful a life situation was over the past month, both of which were used in three studies. The mindful attention awareness scale (22,26,28), which measures mindfulness and the degree of awareness and attention, was used in three studies. The five facet mindfulness questionnaire (23, 34) and the self-compassion scale (26,28), which assesses traits like compassion and care for oneself, were each used in two studies. Regarding family-specific measures, the caregiver quality of life index-cancer, which assesses the QOL of family members of patients with cancer (25, 34), and the caregiver burden reaction assessment were used in two studies, while the self-perceived pressure from informal care (22) was used in one study.

The number of questionnaire assessments typically ranges from two to four, with the timing including a baseline (22,25,26,28,29,32) or initial assessment at the point of consent or enrolment (23,31,34) or orientation (30). Some studies lacked pre-intervention baseline measurements, with initial assessments conducted one (24,33) or two weeks (27) after the start of the intervention. Post-program evaluations were generally carried out at 1 (25) and 3 months after the intervention (22,28). Interviews were immediately conducted after the intervention (23,25,27,31,34), within 1 week (24), or up to 1 year afterward (22). One study was identified that did not provide specific details regarding the timing of assessments.

#### Discussion

Characteristics of MBI-based intervention studies for families of patients with advanced cancer

The number of intervention studies involving MBIs for families of patients with advanced cancer outside the country was limited (13) and predominantly consisted of single-arm before-and-after comparisons. MBSR has been offered to patients with cancer, as well as to those with chronic and psychiatric conditions, since its development by Kabat-Zinn (15). Reviews and metaanalyses across various cancer types and stages have shown its positive impact on patient health (35,36). However, many RCTs remain in the pilot stage, indicating that further evidence is needed to verify its effectiveness.

Twelve of the 13 studies included both patients and family members, while one study focused exclusively on family members. Family members benefit from participating in the program alongside the patient, as it provides them with a better understanding of the disease and allows them to handle challenges that may arise within the family. It is also considered easier for family members whose lives are already adjusted to the patient's treatment schedule to find the time to participate. MBIs require mandatory homework, such as meditation and reflection on home experiences, which can be practiced in a mutually supportive manner. For families with limited mental health resources and time, participating in MBI programs and completing homework assignments may be the only opportunity they have to focus on their own well-being. In addition, group work with family members in similar situations can help participants become more aware of their thoughts and emotions, providing a space for them to share these experiences with others. Therefore, considering family-specific programs that focus on distress and challenges families face while supporting patients with advanced cancer during their recovery is necessary.

#### Customizing the MBI to suit the family situation

In the programs, the duration, number of hours, content, and delivery methods were customized based on the needs of the target group. This customization was done using the MBSR model, which recommends face-to-face sessions lasting 2 to 3 hours once a week for 8 weeks. The meditation and yoga learned during the sessions are meant to be integrated into daily life. However, several studies have explored ways to shorten the program's duration and session length, introducing various innovations, such as online sessions, CDs, apps, and phone calls, in addition to face-to-face sessions. Other elements, such as education on nutrition, grief, advance care planning, and stress management, were also incorporated. Discussions on compassion and presentations on topics, such as chronic obstructive pulmonary disease, were included to enrich the content. Further research is needed to validate the effectiveness of shorter MBI formats, as it remains unclear whether shortened versions of the program can adequately reduce anxiety and depression in clinical settings (14).

The program providers were primarily psychologists, counselors, and facilitators trained in mindfulness, with only one study specifically mentioning a nurse. In contrast, a meta-analysis of MBIs for patients with lung cancer (36) indicated that most providers were nurses. Mindfulness practice and facilitation require a high level of expertise, and most certification training courses for instructors are conducted in Europe and the USA (35). In the future, increasing the number of nurses with mindfulness skills and considering incorporating content that utilizes nurses' unique perspectives on families in MBIs for families of patients with advanced cancer would be beneficial.

Regarding delivery methods, previous studies comparing face-to-face and online practices have reported no significant differences in the effectiveness of interventions. Online interventions, in particular, offer advantages such as greater flexibility in tailoring to the individual needs of patients and promoting autonomy in establishing a mindfulness practice (*37*). Given the widespread use of the Internet, the remarkable evolution of technology, and the proliferation of online projects due to the COVID-19 pandemic, online and app-based MBIs will continue to expand (14). Short, intensive sessions and the use of online services may be especially beneficial for families of patients with advanced cancer, as finding the time to attend in-person MBI sessions can be challenging (*38*).

#### MBI outcome indicators

The 12 included quantitative studies used a combination of multiple scales as the outcome measures. In all 12 of these studies, assessments of anxiety and depression were included, along with subjective measures capturing psychological states, such as stress, posttraumatic stress disorder, resilience, and psychological adjustment. Although several scales have been developed to measure mindfulness, only five studies used them. In addition, only two studies utilized carerspecific measures.

Since individual psychological aspects are inherently personal and subjective, there are limits to evaluating them objectively. Furthermore, as mindfulness itself is highly subjective, it suggests the need for a comprehensive evaluation using multiple scales, tailored to the purpose of the intervention and its outcomes. Mindfulness, being intrinsically subjective, further highlights the need for a comprehensive evaluation using multiple measures, depending on the intervention's purpose and expected outcomes. Furthermore, although cortisol and interleukin-6 analysis and the NicAlert saliva test have been explored, the validity of objective measures in MBIs has not yet been established (17), and further validation is necessary.

#### Study limitations and future challenges

The term "family", as defined in this study, may not sufficiently capture its uses in the literature, as English terminology varies widely based on cultural background, marital status, and other factors. In addition, this study aimed to provide an overview of MBI intervention studies for families of patients with advanced cancer, rather than analyzing the specific effects of each intervention. Therefore, future studies should examine the outcomes of individual intervention programs.

#### Conclusion

This scoping review examined 13 MBI studies conducted outside Japan, targeting families of patients with advanced cancer. Although the framework and content of the programs were based on MBSR, they were adapted to fit the circumstances of the target populations. However, in most studies, families and patients were recruited together, and original programs focusing exclusively on families were underdeveloped. In addition, many studies used before-and-after comparisons or single-group pilot studies, relying primarily on subjective measures, such as anxiety and depression scales. Therefore, additional RCTs are necessary to verify the effectiveness of these programs. Future studies should focus on the needs and challenges faced by the families of patients with advanced cancer, while examining program content and evaluation methods specific to families, incorporating nurses' perspectives.

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# The impact of a health education program on cervical cancer screening uptake: A survey among primary school teachers in Phnom Penh, Cambodia

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Abstract: This study aimed to evaluate the impact of a health education intervention on women's cervical cancer screening uptake. It was conducted using data from the collaborative project by the Cambodian Society of Gynecology and Obstetrics and the Japan Society of Obstetrics and Gynecology to improve cervical cancer services in Cambodia. A prospective observational study was conducted from August 2022 to May 2023, involving 1,538 female teachers from 80 public primary schools in Phnom Penh, Cambodia. A total of 815 participants (intervention group [n = 355] and control group [n = 460]) were eligible for analysis. The intervention group received a tailored health education program and an invitation to register for free cervical cancer screening, while the control group only received the invitation to screening. The intervention group demonstrated a significantly higher screening registration (32.1% vs. 18.8%, p < 0.001) and uptake (24.1% vs. 12.7%, p < 0.001) than the control group. When comparing changes in knowledge and attitude between baseline and endline assessments, the intervention group showed a notable improvement in knowledge regarding the causes, symptoms, prevention, and benefits of early detection of cervical cancer. For instance, the proportion of women who recognized human papillomavirus as the cause of cervical cancer significantly increased in the intervention group (baseline: 23.7%, endline: 57.5%, p < 0.001), while no significant change was observed in the control group (baseline: 24.4%, endline: 29.1%, p = 0.101). In conclusion, the health education program effectively increased cervical cancer screening uptake, knowledge and attitude on cervical cancer. Further improvements in screening uptake may require educational interventions that influence individual health behaviors and systematic encouragement for screening participation.

Keywords: health education, cervical cancer screening, uterine cervical neoplasms, early detection of cancer, Cambodia

#### Introduction

Cervical cancer is caused by persistent infection with high-risk human papillomavirus (HPV) and is largely preventable with HPV vaccination and screening linked to treatment (1). Cervical cancer is the fourth most common cancer in women worldwide, with an estimated 660,000 new cases and 350,000 deaths in 2022. Its incidence and mortality rates are high in low- and middle-income countries as compared with high income countries. The World Health Organization (WHO) reported that this reflects wide disparities due to lack of access to national HPV vaccination, cervical screening and treatment services, and social- and economic-related factors (2).

In Cambodia, cervical cancer continues to be the second most common cancer in women with high mortality as most cases are diagnosed at an advanced stage (3, 4). The estimated age-standardized incidence rate is 15.2 per 100,000 women, and the mortality rate

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is 8.1 per 100,000 women in 2022 (3). In accordance with the global initiative to eliminate cervical cancer, the Cambodian Ministry of Health is strengthening cervical cancer control, as evidenced by the recent introduction of HPV vaccine into the National Immunization Program for 9-year-old girls in October 2023. The number of health centers offering cervical cancer screening using visual inspection with acetic acid has also increased in all provinces. A population-based survey suggests that the uptake of cervical cancer screening in women aged 30-49 years has slightly increased from 14.7% in 2016 to 20.3% in 2023 (5,6). Nevertheless, the rate is far from the global target of 70% (7), with the potential reasons including lack of awareness about cervical cancer, low recognition of the concept of cancer prevention and its measures, and limited recommendations from health professionals (8).

WHO defines health education as "any combination of learning experiences designed to help individuals and communities improve their health by increasing knowledge, influencing motivation and improving health literacy", and a variety of health education approaches have been reported to improve access to cervical cancer screening in national populations from a range of cultural and economic backgrounds (9). A systematic review of seven randomized control trials in 2017 showed that cervical cancer education increased cervical cancer screening rates by more than two-fold (odds ratio: 2.46, 95% confidence interval: 1.88-3.21) (10). Another systematic review of 37 articles including quasiexperimental studies concluded that different health education methods such as phone calls, letters, lectures, group discussions, and brochures, used alone or in combination, are effective in modifying cervical cancer screening behavior (11).

In Cambodia, previous articles about educational intervention for cervical cancer screening are limited to practice reports, and none have quantitatively examined the effect of health education on women's cervical cancer screening uptake (12,13). Between 2019 and 2024, a collaborative project by the Cambodian Society of Gynecology and Obstetrics (SCGO) and the Japan Society of Obstetrics and Gynecology (JSOG) was conducted to improve the quality of cervical cancer services, including health education, screening, and treatment, by targeting female primary school teachers in Phnom Penh city, the capital of Cambodia. Primary school teachers were set as the target because they are potential key influencers of HPV vaccination at schools (14). As a part of this project, we developed a tailored health education program.

This study aimed to evaluate the impact of this health education program on cervical cancer screening test uptake. We also examined the changes in the women's knowledge and attitude about cervical cancer before and after the health education program. The findings of this study could help improve future approaches to the national cervical cancer control program.

#### **Participants and Methods**

#### Study design

A multi-institutional, prospective observational study. This study was conducted using data from the aforementioned project in Phnom Penh City, the capital of Cambodia.

#### Participants

The project site, Phnom Penh city, contained 157 primary schools with 4,094 primary school teachers, of whom 2,935 were women, under 14 district education offices in 2022. The project defined the number of beneficiaries as half of all female teachers at the project site due to budget limitations and feasibility. Therefore, we randomly selected half of all schools as the target schools and invited all female teachers in those schools to participate in this study and those who agreed to participate were included. For cervical cancer screening, we limited women to those aged 30 years old and above and who ever had sexual contact.

#### Randomization

The unit of randomization was primary school. Random sequence numbers were generated using Excel software. First, half of the schools under each district education office were randomly selected as target schools using the generated random numbers. Then, the selected 80 target schools were again allocated by simple randomization to the intervention group or control group. This random allocation was conducted by a Japanese researcher blind to the group assignment and was concealed from the school representatives, as the control group were also given the opportunity to receive the same health education program after completion of the trial.

#### Intervention

The educational materials of the program (*i.e.*, PowerPoint lecture slide and booklet) were developed by the SCGO and JSOG based on the results of a small telephone interview survey conducted prior to study initiation ( $\delta$ ). These included epidemiology of cervical cancer in Cambodia, female anatomy, what cervical cancer is (cause, risk factors, signs and symptoms, prevention methods, treatment, benefits of early detection), available sites for screening, and the cost was free of charge. In addition, information was provided on what to do when the screening result is positive or negative actions taken in case of positive and negative screening results. To ensure that the health education materials were understandable and actionable, we piloted their use among 30 female primary school teachers in cooperation with the Phnom Penh Municipality Department of Education, Youth and Sports (PPMDoEYS) using a checklist made based on the Patient Education Materials Assessment Tool (15).

The health education program was then designed in consultation with PPMDoEYS. It included a 30-minute PowerPoint-based lecture by a gynecologist member of the SCGO along with an information booklet on cervical cancer and screening, 30 minutes of group work on key questions around cervical cancer screening, and a 20-minute question and answer session, which altogether lasted for 2 hours, including a recess. The program was conducted four times over two days, during which the teachers in the intervention group could attend any time between their teaching responsibilities (approximately 200 women per time). The women were then given the booklet on cervical cancer and screening to read at home.

#### Baseline and endline questionnaire

A questionnaire was used to evaluate knowledge, attitude, and practice (KAP) on cervical cancer. It was developed by the authors in English based on previous studies (16,17). This English original was translated into the local language, then back-translated into English to check for consistency, and the final version of the questionnaire was piloted on some teachers (Supplemental File, https:// www.ghmopen.com/site/supplementaldata.html?ID=99). The questions on knowledge asked about the cause, symptoms, prevention methods, and benefits of early detection in single or multiple-choice formats. For attitudes, the perception of cervical cancer was measured using a five-point Likert scale, where 5 indicated "strongly agree" and 1 indicated "strongly disagree". The practice question asked experience of receiving cervical cancer screening and its reason.

#### Study procedure

First, the researchers informed the principal collaborator (*i.e.*, PPMDoEYS) who notified school representatives of the detailed steps of the study process separately for intervention and control clusters to minimization contamination. As a gender consideration, we involved school directors, who are mostly male, to collaborate as facilitators to make it easier for the female teachers to participate in the health education and screening.

At the baseline measurement, all women in the target schools were asked to provide informed consent, and those who agreed to participate in this study were asked to complete either an online or paper-based KAP questionnaire. Then, women in the control group were invited to register for a free cervical cancer screening using an HPV-test at one of the three trained hospitals in the city. Invitations were made through announcement boards for teachers at each school and through existing communication systems (*e.g.*, letter, phone call, instant messaging group app) connecting the primary education office of PPMDoEYS, district education offices, and each school director. Eligible women who opted for a screening test registered online or by phone call and were notified by a research staff member of possible date, time, and location for the test.

Subsequently, women in the intervention group were given the intervention (*i.e.*, health education program) and one week later were invited to register and undergo cervical cancer screening in the same manner as the control group. Three months after completion of the health education program for the intervention group, all women in both groups were asked to complete the same questionnaire used in the baseline survey. The baseline and endline surveys were conducted in September 2022 and May 2023, respectively, with the period between the baseline survey and the endline survey being nine months.

#### Outcomes

Primary outcomes were cervical cancer screening test registration and uptake. Secondary outcomes were changes in knowledge and attitude about cervical cancer.

#### Statistical analysis

All data from the baseline survey, cervical cancer screening registration, attendance, and endline survey were linked and compiled in a Microsoft Excel spreadsheet. Data analysis was performed using STATA SE16 software (Stata Corporation, College Station, TX, USA). Baseline characteristics of the participants, primary outcomes, and secondary outcomes between the intervention group and control group, or baseline and end line data were compared using chi-square, Fisher's exact, McNemar's, Wilcoxon matched-pairs signed-rank, and Student *t*- tests, depending on the type and distribution of the data. Statistical significance was set at p < 0.05.

#### Ethical considerations

The study protocol was approved by the Cambodia National Ethics Committee for Health (183 NECHR) and the ethical committees of the National Center for Global Health and Medicine, Japan (NCGM-S-004516-00). Written informed consent was obtained from all participants.

#### Results

#### Participants

The flow diagram of participants is shown in (Figure 1). Eighty primary schools were randomly selected across 14 district education offices in Phnom Penh city,

of which 41 schools were allocated to the control group and 39 schools to the intervention group. Among 1,538 women in target schools, 988 (control group [n = 542]and intervention group [n = 446]) agreed to participate in the study and completed the baseline survey. After nine months, 815 women (control group [n = 460, 84.9%]and intervention group [n = 355, 79.6%]), completed the endline survey.

#### Baseline characteristics of participants

Among the 815 participants eligible for analysis, 782 were aged 30 years old and above. As shown in Table 1, of the total analyzed, 85.3% (n = 695) of participants were married, 68.5% (n = 558) had graduated from high school or higher, and 96.1% (n = 783) were full-time employees. Despite the random allocation, there were differences in age, history of pregnancy, and number of children, all of which were significantly lower in the intervention group. Mean participant age was  $46.6 (\pm$ 7.8) years in the control group and 44.8 ( $\pm$  7.8) years in the intervention group. The proportion of women ever being pregnant was 90.9% (n = 418) in the control group and 85.6% (n = 304) in the intervention group. The proportion of women having one or more children was 91.1% (n = 419) in the control group and 86.8% (n = 308) in the intervention group. Other baseline characteristics were comparable between the two groups.

#### Cervical cancer screening test registration and uptake

Table 2 presents the numbers and proportions of the 782 women aged 30 years old and above who registered for and underwent a screening test. Both registration (32.1% *vs.* 18.8%, p < 0.001) and uptake (24.1% *vs.* 12.7%, p < 0.001) were significantly higher in the intervention group compared to the control group.

The reasons for those who registered but did not take

the screening test were menstruation, pregnancy, illness, side effects of the COVID-19 vaccine, and not finding a place to undergo the screening.

#### Changes in knowledge and attitude on cervical cancer

Table 3 shows knowledge and attitude on cervical cancer at baseline and endline for the control and intervention groups. At baseline, there were no significant differences in knowledge and attitude between intervention and control groups, except for one question on attitude, "Screening helps prevent cervical cancer", which showed borderline significance (p = 0.0504).

The percentage of women who were aware of HPV being the cause of cervical cancer increased significantly in the intervention group (baseline 23.7%, endline 57.5%, p < 0.001) but not significantly so in the control group (baseline 24.4%, endline 29.1%, p = 0.101). Despite this improvement, 32.7% (n = 116) of the women in the intervention group still selected incorrect answers in the endline questionnaire, including poor genital hygiene 22.5% (n = 80), chemicals in food 5.1% (n = 18), and frequent abortions 5.1% (n = 18).

For the question on symptoms suggestive of cervical cancer, at baseline, one-third of the women selected "Do not know" (control 38.5%, intervention 33.0%) and "Itching of the vagina" (control 30.0%, intervention 33.8%). However, at the endline, the proportion of women who chose the correct answers significantly increased in the intervention group ("Bleeding from vagina after sexual contact" (baseline 13.0%, endline 28.5%, p < 0.0001), "Bleeding from vagina between menstrual cycle or after menopause" (baseline 15.5%, endline 27.6%, p = 0.0001), and "Discharge from vagina that smells bad" (baseline 21.7%, endline 31.8%, p = 0.0014).

Most women had good knowledge about the two prevention methods at baseline, although recognition was



Figure 1. Flow diagram of participants.

#### Table 1. Baseline characteristics of the participants

	Total	Control	Intervention	
Variable	n = 815	n = 460	n = 355	<i>p</i> value
	n (%)	n (%)	n (%)	
Age (years), mean $\pm$ SD	$45.8\pm7.9$	$46.6\pm7.8$	$44.8\pm7.8$	0.002 <sup>a</sup>
≤ 29	33 (4.1)	18 (3.9)	15 (4.2)	
30-39	117 (14.4)	51 (11.1)	66 (18.6)	
40-49	342 (42.0)	190 (41.3)	152 (42.8)	
50-59	323 (39.6)	201 (43.7)	122 (34.4)	
> 59	0	0	0	
Highest level of school attended				
Secondary school	257 (31.5)	133 (28.9)	124 (34.9)	0.064 <sup>b</sup>
High school	432 (53.0)	246 (53.5)	186 (52.4)	
College or higher	126 (15.5)	81 (17.6)	45 (12.7)	
Others	0 (0)	0 (0)	0 (0)	
Employment status		. /		
Employee (full-time)	783 (96.1)	443 (96.3)	340 (95.8)	0.914 <sup>b</sup>
Employee (part-time)	9 (1.1)	5 (1.1)	4 (1.1)	
Others	23 (2.8)	12 (2.6)	11 (3.1)	
Marital status				
Married	695 (85.3)	389 (84.6)	306 (86.2)	0.330 <sup>b</sup>
Single	50 (6.1)	26 (5.7)	24 (6.8)	
Divorced or widowed	70 (8.6)	45 (9.8)	25 (7.0)	
Ever pregnant				
Yes	722 (88.6)	418 (90.9)	304 (85.6)	0.020 <sup>b</sup>
No	93 (11.4)	42 (9.1)	51 (14.4)	
Number of children	· /			
0	88 (10.8)	41 (8.9)	47 (13.2)	0.033 <sup>b</sup>
≧1	727 (89.2)	419 (91.1)	308 (86.8)	

<sup>a</sup>t-test; <sup>b</sup>Chi-square test.

Table 2. Cervica	l cancer screening	registration and	uptake (Women	aged 30 years	and above)
		0			

Variable	Total n = 782 n (%)	Control n = 442 n (%)	Intervention n = 340 n (%)	<i>p</i> values (Chi-square test)
Registration for a screening test	192 (24.6)	83 (18.8)	109 (32.1)	< 0.001
Screening test uptake	138 (17.7)	56 (12.7)	82 (24.1)	< 0.001

higher for HPV vaccination (control 60.9%, intervention 64.8%) than for screening (control 43.9%, intervention 41.4%). At endline, women who selected HPV vaccination significantly increased in both groups (control group [baseline 60.9%, endline 70.4%, p = 0.0011] and intervention group [baseline 64.8%, endline 75.5%, p = 0.0012]). However, the women who selected screening as a preventive method at endline increased significantly only in the intervention group (baseline 41.4%, endline 54.7%, p = 0.0001).

The proportion of women who thought that cervical cancer could be cured if found early increased significantly in the intervention group (baseline 87.3%, endline 94.9%, p < 0.001), whereas it did not in the control group (baseline 85.0%, endline 86.7%, p = 0.732).

Attitude scores were basically high at baseline in both groups. Of the four questions, the mean score for the question "Do you think you have a chance of getting cervical cancer?" increased significantly at endline in the intervention group (baseline  $3.58 \pm 1.11$ , endline  $3.79 \pm 0.90$ , p = 0.0044) but not in the control group (baseline  $3.57 \pm 1.10$ , endline  $3.64 \pm 0.90$ , p = 0.5846). The scores of women who answered positively to "Do you think cervical cancer is a serious disease?" and "Do you think screening helps to prevent cervical cancer?" were significantly increased in the control group only at endline. The score for "Do you think it is helpful for you to detect early cervical cancer?" was increased in both groups at endline.

#### Reasons for not attending cervical cancer screening

Table 4 shows the reasons for those who answered "No" to the question "Have you ever had a screening for cervical cancer?" at baseline and endline. The reasons given in the control and intervention groups also were compared at endline.

Most women in both groups cited being healthy as the reason at baseline. However, the proportion of women who cited this reason significantly decreased in the intervention group (baseline 36.8%, endline 26.2%, p= 0.025), whereas it did not in the control group (baseline

#### Table 3. Difference in knowledge and attitude on cervical cancer over time

	С	ontrol $(n = 460)$	)	Inte	rvention $(n = 3.5)$	55)
Variable	Baseline n (%)	End line n (%)	p values	Baseline n (%)	End line <i>n</i> (%)	<i>p</i> values
Knowledge: cause of cervical cancer (single-choice)			0.101			< 0.001 <sup>a</sup>
Human papillomavirus (correct)	112 (24.4)	134 (29.1)		84 (23.7)	204 (57.5)	
Poor genital hygiene (incorrect)	174 (37.8)	108 (23.5)		132 (37.2)	80 (22.5)	
Chemicals in food (incorrect)	35 (7.6)	33 (7.2)		44 (12.4)	18 (5.1)	
Frequent abortion (incorrect)	46 (10.0)	34 (7.4)		30 (8.5)	18 (5.1)	
Other than above (incorrect)	0 (0)	3 (0.65)		2 (0.56)	0 (0)	
Do not know	93 (20.2)	148 (32.2)		63 (17.7)	35 (9.9)	
<i>Knowledge: symptom of cervical cancer (multiple-choice)</i>						
Bleeding from vagina after sexual contact (correct)	56 (12.2)	73 (15.9)	0.125 <sup>b</sup>	46 (13.0)	101 (28.5)	$< 0.0001^{b}$
Bleeding from vagina between menstrual cycle or after menopause (correct)	78 (17.0)	73 (15.9)	0.719 <sup>b</sup>	55 (15.5)	98 (27.6)	0.0001 <sup>b</sup>
Discharge from vagina that smells bad (correct)	79 (17.2)	100 (21.7)	$0.085^{b}$	77 (21.7)	113 (31.8)	$0.0014^{b}$
Itching of vagina (incorrect)	138 (30.0)	72 (15.7)	$< 0.0001^{b}$	120 (33.8)	86 (24.2)	$0.0020^{b}$
Do not know	177 (38.5)	205 (44.6)	0.045 <sup>b</sup>	117 (33.0)	62 (17.5)	$< 0.0001^{b}$
Knowledge: prevention methods (multiple-choice)						
Get HPV vaccination when you are young (correct)	280 (60.9)	324 (70.4)	0.0011 <sup>b</sup>	230 (64.8)	268 (75.5)	0.0012 <sup>b</sup>
Get HPV vaccination when you are 30 years old and above ( <i>incorrect</i> )	78 (17.0)	74 (16.1)	0.7644 <sup>b</sup>	52 (14.7)	50 (14.1)	0.9179 <sup>b</sup>
Visit a health facility regularly and get screened when you are 30 years old and above (correct)	202 (43.9)	187 (40.7)	0.3185 <sup>b</sup>	147 (41.4)	194 (54.7)	0.0001 <sup>b</sup>
Visit a health facility when you feel very sick or a lot of bleeding from vagina <i>(incorrect)</i>	62 (13.5)	47 (10.2)	0.1374 <sup>b</sup>	48 (13.5)	36 (10.1)	0.1753 <sup>b</sup>
Eat healthy food <i>(incorrect)</i>	56 (12.2)	44 (9.6)	$0.2067^{b}$	38 (10.7)	31 (8.7)	$0.4270^{b}$
Keep genital hygiene (incorrect)	127 (27.6)	93 (20.2)	$0.0054^{b}$	103 (29.0)	83 (23.4)	$0.0978^{b}$
Do not know	63 (13.7)	49 (10.7)	$0.1750^{b}$	38 (10.7)	13 (3.7)	0.0001 <sup>b</sup>
Knowledge: benefit of early detection (single-choice)						
Cervical cancer be cured if found early (one)						
True	391 (85.0)	399 (86.7)	0.732 <sup>a</sup>	310 (87.3)	337 (94.9)	$< 0.001^{a}$
False	10 (2.2)	8 (1.7)		6(1.7)	6 (1.7)	
Do not know	59 (12.8)	53 (11.5)		39 (11.0)	12 (3.4)	
Attitude (scale from 1 to 5) Meman $\pm$ SD						
Do you think you have a chance of getting cervical cancer?	$3.57 \pm 1.10$	$3.64\pm0.90$	0.5846 <sup>c</sup>	$3.58 \pm 1.11$	$3.79 \pm 0.90$	0.0044 <sup>c</sup>
Do you think cervical cancer is a serious disease?	$4.30\pm0.95$	$4.47\pm0.76$	$0.0050^{\circ}$	$4.32\pm0.90$	$4.34\pm0.79$	0.8775°
Do you think it is helpful for you to detect cervical cancer early?	$4.39\pm0.86$	$4.55\pm0.65$	0.0059 <sup>c</sup>	$4.45\pm0.81$	$4.65\pm0.52$	0.0005°
Do you think screening helps to prevent cervical cancer?	$4.05\pm0.97$	$4.23\pm0.77$	0.0092°	$4.18\pm0.92$	$4.30\pm0.74$	0.1588°

<sup>a</sup>Chi-square test; <sup>b</sup>McNemar's test; <sup>c</sup>Wilcoxon matched-pairs signed-rank test.

41.4%, endline 39.9%, p = 0.784). The second most common reason for not having been screened was feeling shy. The proportion of women who gave this reason increased significantly in the control group (baseline 20.0%, endline 28.3%, p = 0.025). It also increased in the intervention group although not significantly so (baseline 25.0%, endline 33.1%, p = 0.077).

When comparing the reasons at endline between the control group and intervention group, the proportion of women who answered "I am healthy" was significantly lower in the intervention group than in the control group (control 39.9%, intervention 26.2%, p = 0.003). However, the proportion of women who answered "I feel shy" remained unchanged (control 28.3%, intervention 33.1%, p = 0.284).

#### Discussion

This study evaluated the impact of a health education

intervention on cervical cancer screening uptake among female primary school teachers in Phnom Penh, Cambodia. Results showed that our health education program, which included a lecture by a physician, peer group discussion, and question-and-answer session, nearly doubled cervical cancer screening test uptake. It also led to a notable improvement in knowledge regarding causes, symptoms, prevention, and benefits of early detection of cervical cancer.

To our knowledge, this is the first study to quantitatively examine the effect of health education on cervical cancer screening uptake among female primary school teachers in Cambodia. Prior to initiation of this study, we conducted a literature search using PubMed and Google scholar with the following keywords: health education, cervical cancer screening, uterine cervical neoplasms, early detection of cancer, and Cambodia. This search yielded 19 relevant studies, there is evidence that narrative interventions can influence HPV vaccination

		Control		I	ntervention		Control vs.
Variable	Baseline n (%) n = 275	End line <i>n</i> (%) <i>n</i> = 258	<i>p</i> values	Baseline n (%) n = 220	End line <i>n</i> (%) <i>n</i> = 172	<i>p</i> values	Intervention at endline p values
I am healthy	113 (41.1)	103 (39.9)	0.784	81 (36.8)	45 (26.2)	0.025	0.003
It may be painful	12 (4.4)	10 (3.9)	0.777	14 (6.4)	14 (8.1)	0.498	0.059
I feel shy	55 (20.0)	73 (28.3)	0.025	55 (25.0)	57 (33.1)	0.077	0.284
I do not know where to receive screening	51 (18.6)	52 (20.2)	0.638	42 (19.1)	32 (18.6)	0.903	0.691
I'm busy (No time to go to gynecologist)	31 (11.3)	28 (10.9)	0.877	33 (15.0)	25 (14.5)	0.898	0.255
It is expensive	42 (15.3)	36 (14.0)	0.667	49 (22.3)	28 (16.3)	0.138	0.507
Others	4 (1.5)	0(0)	0.124F	3 (1.4)	2 (1.2)	1.000F	

Table 4. Reasons for those who answered "No" to the question "Have you ever had a screening for cervical cancer?" at Baseline and End line *(multiple-choice)* 

<sup>a</sup>Chi-square test; F: Fisher's exact test.

behavior (18) and that culturally adapted health education impacts cervical cancer screening among Cambodian women in the United States (19). However, no studies have examined the effect of health education on cervical cancer screening uptake.

Our finding that health education programs increase cervical cancer screening uptake is consistent with existing research. A systematic review indicated that health education interventions contribute to boosting the screening uptake and intentions to screening (11,20). However, their effectiveness varied by study design and population, and which forms are most effective have not been reported (21).

Another systematic review with positive outcomes classified diversified health education interventions into three types, individual level, community level, and culturally sensitive (for immigrants), and showed how these types can increase screening uptake (20). Individual-level interventions refer to intensive behavioral intervention, minimal intervention focused on invitations, and one-to-one interactive educational programs. These interventions target changes at the individual level, such as modifying an individual's knowledge, attitudes, skills, and behaviors regarding health and affect behavior more directly. Communitylevel interventions include community-based radio broadcasts, structured lectures for practical sections, school health promotions, and education for lay health workers. The effectiveness of these interventions lies in their "cue to action", which raises awareness and knowledge. This has a significant effect in boosting screening uptake and in increasing knowledge about screening (22). Culturally sensitive interventions refer to culturally sensitive videos, educational pamphlets, invitations, reminders, culturally targeted interventions, and community gathering strategies that boost screening test uptake for cervical cancer. These are crucial for providing equitable, effective service for diverse immigrant communities and minorities by accounting for their unique cultural contexts, beliefs, barriers, and needs. Among these three types, our health education program is a community-level intervention aimed at increasing

awareness and knowledge and provoking a "cue to action" for women to participate in screening. To further increase screening test uptake, it may be necessary to consider individual-level interventions that more directly influence behavior.

In our study, feeling healthy and embarrassment were the most common major reasons for not undergoing screening. Although screening uptake was increased in the intervention group, 67.9% of women did not register and 75.9% did not undergo screening. In other previous studies, embarrassment was also identified as a common reason for not undergoing cervical cancer screening, as were feeling healthy, fear of unfavorable test results, lack of time, and feelings of discomfort with the gynecologic examination (23-25). After health education, feeling healthy was significantly decreased in the intervention group, but the number of women who felt "embarrassed" remained the same. Self-sampling has been tried around the world as one solution to address embarrassment, and in Cambodia, self-sampling has been proven to produce the same results as physician-sampling (26). In the present study, self-sampling was also an option for screening, but it was given to women at the hospital. It might be efficacious to consider allowing women to selfsample at the health education site or at home without going to the hospital.

This study also showed that the health education program helped women gain more knowledge on the cause, symptoms, preventative measures, and benefit of early detection. Their attitude changed with the realization that anyone has a chance of getting cervical cancer, and it has enabled them to think about the disease as their own problem. According to the seven stages of the Precautionary Adoption Process Model, the stage at which a person becomes able to view cervical cancer as their own problem is considered stage 1 or 2 of moving "from unawareness to awareness" (27). This recognition is an important initial step that precedes subsequent stages of deciding how to seek screening. For another question, "Do you think screening helps to prevent cervical cancer?", the score was already high at baseline, and therefore, even if the score increased at endline, it

may not have been statistically significant. This may indicate a characteristic of schoolteachers, a highly conscientious group in society.

Although our health education program improved screening uptake among female primary school teachers, the overall rate was still just over 20%. A future challenge will be to increase this percentage. To improve cancer screening, it is important to provide health education as well as systematic screening invitations to the target population according to the WHO Report on Cancer 2020. When encouraging women to undergo cervical cancer screenings in the future, we should consider the ways of delivering information individually, such as a personal invitation letter with detailed information, followed by a phone reminder, in which information is delivered individually. In this study, the screening invitation was provided through announcement boards for teachers at each school and by other existing communication systems, but it was not necessarily a way for all eligible women to receive individual invitations. A review of individual invitations and reminders (callrecall system) showed an improvement in uptake (10). However, sending invitation letters is applicable in settings with well-organized postal systems (10,28), but is challenging in countries where postal codes do not work well. One way to overcome this issue is to incorporate health education and screenings into workplace health checkups. A systematic review of interventions to increase breast and cervical cancer screening uptake in Asian women reported that the combination of workplace-based group education programs with mobile screening services and attending screenings was effective in the promotion of breast and cervical cancer screening uptake (29).

#### Strength and limitations

The strength of this study was that we quantitatively examined the effect of health education on cervical cancer screening uptake in Cambodia. The present results may provide suggestions for future interventions in Cambodia. However, several limitations must be noted. First, we only targeted female primary school teachers living in the capital city, higher level of education and socioeconomic status, and thus, the study findings may not be replicable for the general female population in Cambodia. Second, female primary school teachers are a highly educated group, and their situation might be different from that of marginalized populations. Third, the process of the baseline questionnaire, screening registration, and endline questionnaire may have been complicated for the participants.

#### Conclusions

This study showed that providing a combination of

health education programs and invitation for screening could increase cervical cancer screening test uptake by two-fold. To further increase screening test uptake, individual-level educational interventions that more directly influence behavior and systematic invitations to screening may be needed. In addition, while expanding health education, further development of screening capacity through increasing the number of facilities and human resources is necessary.

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# Factors associated with withholding of invasive mechanical ventilation in the early phase of the COVID-19 response and their ethical analyses

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Abstract: End-of-life decision making regarding invasive mechanical ventilation (IMV) for patients with severe coronavirus disease (COVID-19) is challenging. We aimed to explore the factors associated with the withholding of IMV in patients with COVID-19. This retrospective study included patients registered in a nationwide COVID-19 Registry Japan. We enrolled patients with COVID-19 admitted between January 1, 2020, and June 30, 2021, and died during hospitalization. The enrolled patients were divided into two groups: those who received IMV (IMV group) and those who did not (non-IMV group). To identify the factors associated with withholding of IMV among patients with COVID-19 who died during hospitalization, we conducted a multivariate logistic regression analysis. A total of 2,401 patients were enrolled. Of these, 588 (24.5%) were in the IMV group and 1813 (75.5%) in the non-IMV group. Withholding IMV was positively associated with older age (95% confidence interval [CI]: 0.82-0.88, p < 0.0001), dementia (95% CI: 0.81–0.91, p < 0.0001), chronic lung disease (95% CI: 0.88–1.00, p = 0.036), and malignancy (95% CI: 0.82–0.94, p < 0.0004) although inversely associated with male sex (95% CI: 1.04–1.15, p = 0.0008), body mass index (95% CI: 1.01–1.02, p < 0.0001), and National Early Warning Score (95% CI: 1.01–1.03, p < 0.0001). We subsequently analyzed these results to inform preparedness for future emerging infectious disease pandemics by retrospectively examining the decision-making processes during the COVID-19 crisis, with particular attention to the role of multidisciplinary collaboration. Based on this study, it will be essential in future pandemics to assess decisions concerning life-sustaining treatments, including IMV, from both scientific and ethical perspectives.

Keywords: decision-making, end-of-life, severe COVID-19, principles of biomedical ethics

#### Introduction

End-of-life decision making is challenging among patients with severe coronavirus disease (COVID-19). One of the clinical features of COVID-19 is the sudden progression of respiratory failure around the 7th day of onset (1), which does not allow medical staff adequate time to discuss treatment goals and plans with patients and their families. Moreover, family members are often unable to communicate because of their own infection and hospital visitation restrictions, which further complicate the decision-making process (2). In addition, there was little evidence on the management of COVID-19, especially in the early phases of the COVID-19 response (3,4). Critical care teams may experience ethical challenges when making decisions about whether to intubate patients with COVID-19, as their prognosis is uncertain and the availability of ventilators and critical care beds may be limited (5). The decision to perform tracheal intubation within a limited period is challenging for healthcare providers.

In this study, we explored the factors associated with the withholding of invasive mechanical ventilation (IMV) to prepare for future emerging infectious disease pandemics by retrospectively examining the treatment decision-making process during the

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COVID-19 pandemic and considering multidisciplinary collaboration, including palliative care teams.

#### **Materials and Methods**

#### Study design

This retrospective study included patients registered in a nationwide Japanese registry, COVID-19 Registry Japan (COVIREGI-JP) (4). In this registry, patients diagnosed with COVID-19 (positive for severe acute respiratory syndrome coronavirus-2 rapid antigen or polymerase chain reaction test) and hospitalized in 641 participating healthcare facilities were enrolled. Research collaborators at each facility manually input data into the registry by referring to medical records. The study data were collected and managed using REDCap (Research Electronic Data Capture), a secure web-based data capture application hosted at JCRAC data center of the National Center for Global Health and Medicine. The study protocol was reviewed and approved by the Research Ethics Committee of the National Center for Global Health and Medicine (NCGM) (NCGM-G-003494-0). The study was conducted in accordance with the principles of the Declaration of Helsinki. The opt-out recruitment method was applied, and informed consents for individuals were waived as approved by the NCGM Ethics Review.

#### Patients

Of the patients registered in COVIREGI-JP, we enrolled patients with COVID-19 admitted between January 1, 2020, and June 30, 2021, and died during hospitalization. The enrolled patients were divided into two groups: patients who received IMV (IMV group) and patients who did not receive IMV (non-IMV group).

#### Variables investigated

Patient demographics, including sex, age, smoking and drinking history, and underlying medical conditions, were investigated. The National Early Warning Score (NEWS) is a validated early warning scoring system comprising six physiological measurements (respiratory rate, oxygen saturation, body temperature, systolic blood pressure, heart rate, and level of consciousness) used to assess patients at risk of early exacerbation. The NEWS determines the triage category for a clinical alert, requiring clinician assessment based on the following score levels: low (1-4), medium (5-6), and high (7 or more) (6). Respiratory support with the highest dose of oxygen during hospitalization was classified into five categories: no oxygen, cannula/mask/reservoir, nasal high-flow, non-invasive positive pressure ventilation, and artificial respirator. Medical burden/distress was assessed

based on the state of emergency at hospital admission. In addition, transfer from other institutions and the number of days from symptom onset to admission, days from admission to IMV, and days from admission to death were investigated.

#### Statistical analysis

Categorical variables are presented as counts (%), while continuous variables are presented as median and interquartile range (IQR). Fisher's exact test was used for categorical variables and Wilcoxon rank sum test for continuous variables. To identify the factors associated with withholding IMV in patients with COVID-19 who died during hospitalization, we conducted a multivariate logistic regression analysis and obtained adjusted odds ratios (ORs) with 95% confidence intervals (CIs). We included participant characteristics and disease severity (age, sex, body mass index [BMI], high-risk comorbidity, and NEWS) as independent variables according to the clinical implications and previous literature (7).

The level of significance for all statistical tests was set at  $\alpha = 0.05$ . Data were analyzed using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

#### Results

A total of 2,401 patients were enrolled in this study. Of these, 588 (24.5%) were in the IMV group and 1813 (75.5%) in the non-IMV group. Patient demographics, NEWS on admission, state of emergency at hospital admission, respiratory support with the highest dose of oxygen during hospitalization, days from symptom onset to admission, transfer from another institution, days from admission to IMV, and days from admission to death are shown in Table 1. Among the patients, 1,469 (61.2%) were male. The median age of the IMV group was lower than that of the non-IMV group (74 vs. 85 years, p <0.001). The median BMI was higher in the IMV group than in the non-IMV group (24.3 vs. 21.6, p < 0.001). In the IMV group, 151 patients (25.9%) did not receive oxygen support upon admission. Two hundred and fortynine patients (42.3%) in the IMV group and 829 patients (45.7%) in the non-IMV group were admitted during the state of emergency (p = 0.161). The median number of days (IQR) from onset to admission in the IMV and non-IMV groups were 2(0, 5) and 6(3, 9) days, respectively (p < 0.001). Two hundred and fifty patients (43.3%) in the IMV group and 306 (17.3%) in the non-IMV group were transferred from other healthcare facilities (p < 0.001). The median number of days (IQR) from admission to IMV in the IMV group was 1 (0, 5). The median number of days (IQR) from admission to death in the IMV and non-IMV groups were 20 (12, 32) and 14 (8, 24), respectively (p < 0.001).

The results of the multivariate logistic regression

Table 1. Patient demographics, NEWS on admission, state of emergency at hospital admission, respiratory support with the highest dose of oxygen during hospitalization, days from symptom onset to admission, transfer from another institution, days from admission to IMV, and days from admission to death (n = 2,401)

		Non-IMV group	IMV group	Total	p value
Number of patients		1,813	588	2,401	
Demographics					
Sex	Male <sup>a</sup>	1,045 (57.6)	424 (72.1)	1,469 (61.2)	< 0.001
	Female <sup>a</sup>	768 (42.4)	164 (27.9)	932 (38.8)	
Age	Median [IQR]	85 [79, 90]	74 [68, 80]	83 [76, 88]	< 0.001
Smoking history (former or current smoker)	$n, (\%)^{a}$	505 (27.9)	248 (42.2)	753 (31.4)	< 0.001
Drinking alcohol (daily or occasionally)	$n, (\%)^{a}$	276 (15.4)	165 (28.9)	441 (18.6)	< 0.001
BMI	Median [IQR]	21.6 [19, 24.4]	24.3 [22, 27]	22.5 [19.5, 25.3]	< 0.001
Days from symptom onset to admission	Median [IQR]	2 [0, 5]	6 [3, 9]	3 [1, 7]	< 0.001
Transfer from other institution	$n, (\%)^{a}$	306 (17.3)	250 (43.3)	556 (23.7)	< 0.001
Admission to ICU	$n, (\%)^{a}$	220 (12.1)	495 (84.2)	715 (29.8)	< 0.001
Days from admission to ICU	Median [IQR]	0 [0, 3]	0 [0, 2]	0 [0, 3]	0.13
Days from admission to IMV	Median [IQR]	N/A	1 [0, 5]	1 [0, 5]	-
Days from admission to death	Median [IQR]	14 [8, 24.2]	20 [12, 32]	15 [9, 27]	< 0.001
Underlying medical conditions					
Myocardial infarction/Congestive heart failure	$n, (\%)^{a}$	364 (20.1)	77 (13.1)	441 (18.4)	< 0.001
Cerebrovascular disease	$n_{1}(0/2)^{a}$	385 (21.2)	76 (12.9)	461 (19.2)	< 0.001
Paralysis	$n_{1}(9)^{a}$	89 (4.9)	12(2)	101 (4.2)	0.001
Dementia	$n_{1}(2^{\circ})^{a}$	633 (34.9)	42 (7.1)	675 (28.1)	< 0.001
COPD or other lung disease	$n_{\rm e} (\%)^{\rm a}$	295 (16.3)	95 (16.2)	390 (16.2)	0.943
Liver disease	$n. (\%)^{a}$	79 (4.4)	29 (4.9)	108 (4.5)	0.552
Hypertension	$n_{\rm e} \left(\frac{0}{2}\right)^{\rm a}$	890 (49.1)	296 (50.3)	1.186 (49.4)	0.600
Diabetes Mellitus	$n. (\%)^{a}$	506 (27.9)	233 (39.6)	739 (30.8)	< 0.001
CKD or HD	$n. (\%)^{a}$	165 (9.1)	75 (12.8)	240 (10)	0.013
Malignancy	$n. (\%)^{a}$	304 (16.8)	63 (10.7)	367 (15.3)	< 0.001
HIV/AIDS	$n, (\%)^{a}$	2 (0.1)	0 (0)	2 (0.1)	1.000
Conditions at admission					
NEWS	$0-4 n, (\%)^{a}$	567 (31.3)	139 (23.6)	706 (29.4)	< 0.001
	$5-6 n, (\%)^{a}$	280 (15.4)	124 (21.1)	404 (16.8)	
	$7 n, (\%)^{a}$	424 (23.4)	221 (37.6)	645 (26.9)	
	Unknown $n$ , (%) <sup>a</sup>	542 (29.9)	104 (17.7)	646 (26.9)	
Maximum oxygen support during	No oxygen $n$ , $(\%)^a$	63 (3.5)	0 (0)	63 (2.6)	< 0.001
hospitalization	Canula/Mask/Reservoir $n$ , (%) <sup>a</sup>	1,356 (77.5)	0 (0.0)	1,356 (58)	
	Nasal high-flow $n$ , $(\%)^{a}$	320 (18.3)	0 (0.0)	320 (13.7)	
	Non-invasive positive pressure ventilation $n$ , (%) <sup>a</sup>	74 (4.2)	0 (0.0)	74 (3.2)	
	Artificial respirator $n$ , (%) <sup>a</sup>	0 (0.0)	531 (90.3)	531 (22.7)	
State of emergency on admission	$n, (\%)^{a}$	829 (45.7)	249 (42.3)	1,078 (44.9)	0.161

<sup>a</sup>The denominator in each category depends on the number of missing values. Abbreviations: IMV, invasive mechanical ventilation; NEWS, National Early Warning Score; IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; N/A, not available; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HD, hemodialysis; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

analysis, including ORs and 95% CIs, of the factors associated with withholding IMV among patients with COVID-19 who died during hospitalization are shown in Table 2. Withholding IMV was positively associated with older age (0.85, 95% CI: 0.82–0.88, p < 0.0001), dementia (0.86, 95% CI: 0.81–0.91, p < 0.0001), chronic lung disease (0.94, 95% CI: 0.88–1.00, p = 0.036), and malignancy (0.88, 95% CI: 0.82–0.94, p < 0.0004), but was inversely associated with male sex (1.09, 95% CI: 1.04–1.15, p = 0.0008), BMI (1.02. 95% CI: 1.01–1.02, p < 0.0001), and NEWS (1.02, 95% CI: 1.01–1.03, p < 0.0001).

#### Discussion

We analyzed the results obtained in this study based on the four principles of biomedical ethics: respect for autonomy, non-maleficence, beneficence, and justice ( $\delta$ ). The first principle requires medical professionals to respect the autonomous choices of patients, the second to do no harm to patients, the third to provide clinical benefits to patients, and the fourth to distribute burdens, benefits, and opportunities in a fair, equitable, and appropriate way. Although some authors have pointed out their limitations such as their applicability in actual

Table 2. Factors associated with the withholding	of invasive mechanical	ventilation in the early	y phase of COVID-19
response — Multivariable logistic regression ( $n = 2, 4$	,401)		

Variables	Odds ratio	95% CI	<i>p</i> value
Age	0.85	[0.82, 0.88]	< 0.0001
Sex Male	1.09	[1.04, 1.15]	0.0008
BMI	1.02	[1.01, 1.02]	< 0.0001
NEWS	1.02	[1.01 1.03]	< 0.0001
Myocardial infarction/Congestive heart failure	1.00	[0.94, 1.06]	0.9202
Cerebrovascular disease	0.95	[0.89, 1.01]	0.1279
Paralysis	0.93	[0.81, 1.06]	0.2673
Dementia	0.86	[0.81, 0.91]	< 0.0001
COPD or other lung disease	0.94	[0.88, 1.00]	0.0360
Liver disease	1.05	[0.94, 1.17]	0.3732
Hypertension	1.00	[0.95, 1.05]	0.9847
Diabetes Mellitus	1.04	[0.99, 1.09]	0.1684
CKD or HD	1.01	[0.93, 1.09]	0.8750
Malignancy	0.88	[0.82, 0.94]	0.0004
HIV/AIDS	0.60	[0.34, 1.05]	0.0757
State of emergency on admission	0.97	[0.34, 1.05]	0.1713

Abbreviations: COVID-19, coronavirus disease 2019; CI, confidence interval; BMI, body mass index; NEWS, National Early Warning Score; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; HD, hemodialysis; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

situations, no bioethicist can deny that the principles have been very influential in the field of bioethics or medical ethics and have been used worldwide since 1979 (9,10). In addition, according to some bioethicists, the principles "afford a good and useful moral framework for practicing good medical ethics" (11).

First, patients in the IMV group were intubated for a median of 1 day after admission. The rate of transfer from other institutions was 17.3% in the non-IMV group and 43.3% in the IMV group. It is possible that patients were transferred for intensive care, including intubation management, which may explain why patients in the IMV group were intubated early (median, 1 day) after admission.

Although there is a flowchart for allocating ventilators in COVID-19 care (12), in reality, many cases cannot be covered by the flowchart owing to individual circumstances. In particular, decision-making immediately after the arrival of critically ill patients is challenging (13, 14). Physicians have a professional duty to pursue the best interests of their patients, which implies that they should adhere to the principle of beneficence. However, physicians must consider not only the clinical benefits of patients from a medical standpoint but also the patient's own view of life and values (13). In this case, patients must express their own values and make choices of medical treatment; however, chances are that they lack a clear understanding of their own values. If that is the case, physicians must then hold a conversation with the patient and understand the patient's intentions. This process is also linked with respect for the patient's autonomy. With regard to the principle of respect for autonomy, physicians and patients should discuss their attitudes towards a disease and treatment (15). If the patient is unconscious and incapable of

making decisions, physicians have no choice but to infer the patient's intention through proxy/surrogate decisionmaking by family members and relatives. Among patients with COVID-19, however, it is difficult to discuss goals of care in cases of rapidly progressing respiratory failure (16). Moreover, sufficient discussion with the patient on the decision to implement IMV is not always possible due to the rapid progression of the disease (17) and limited opportunities for face-to-face discussion (2). Furthermore, the family member who could serve as a surrogate is isolated following exposure to the disease (18). In consequence, the medical professionals have difficulty in communicating adequately with patients and their families during the acute stage of COVID-19. It is thus possible to infer that the physicians may end up giving priority to the principle of beneficence, or that of nonmaleficence in severe and life-threatening cases over the principle of respect for autonomy in such a situation where urgent medical decision to provide IMV is needed (19).

Second, older age, dementia, underlying chronic lung disease, and malignancy were associated with withholding IMV. From a medical perspective, advanced age, underlying lung disease, and malignancy are risk factors for COVID-19 severity and mortality. When intubated, the mortality rate was 34.8% for patients aged 65–74 years, 43.5% for those aged 75–89 years, and 75% for those aged 90 years. Mortality rates were 29.8% and 38.3% in patients with chronic lung disease and malignancy, respectively (4). Patients with these characteristics have a high mortality rate even if IMV is performed, and it is unlikely that IMV would be of clinical benefit to them. In light of the principles of beneficence, there is little rationale for performing IMV in older patients with underlying chronic lung diseases and malignancies. Moreover, since IMV is an invasive procedure, and considering the "do no harm to patients" principle or the principle of nonmaleficence, IMV should be avoided if possible. Thus, performing IMV in older patients, those with underlying chronic lung disease, or those with malignancy is not only unlikely to provide clinical benefit but is also likely to impair clinical benefit, that is, increase the risk of adverse health outcomes. Therefore, it is possible to infer that the healthcare providers tend to withhold IMV from older patients and those with underlying chronic lung disease or malignancy. However, the range of malignant conditions varies between patients undergoing curative postoperative chemotherapy and those in the terminal stages of the disease, underscoring the need for individualized decision-making.

Dementia has also been reported as an independent risk factor for mortality (20). Since it is difficult to obtain informed consent from patients with dementia, the focus shifts to the patient's family members or relatives who can provide proxy consent for IMV. However, as mentioned above, it is difficult to have a discussion with the patient's family members and relatives in the acute phase of COVID-19. Therefore, it can be inferred that for patients with backgrounds, such as advanced age, dementia, underlying chronic lung disease, and malignancy, the principles of beneficence and nonmaleficence, rather than the principle of respect for autonomy, took precedence in medical practice, resulting in a tendency to avoid IMV.

Third, non-obese status and female sex were associated with withholding of IMV. These results may be due to several reasons. One, as obesity and male sex are risk factors for severe COVID-19, women with nonobese status are at a lower risk of severe disease and are less likely to develop respiratory failure. Therefore, the clinical benefits of IMV may have been judged to be low. Given the principle of beneficence, there is little rationale for aggressively implementing IMV. Moreover, as IMV is an invasive procedure, it should be avoided according to the principle of nonmaleficence. Thus, IMV in nonobese women was possibly withheld because of its low clinical benefit and high risk of adverse health outcomes. Two, IMV was also withheld in older, non-obese, and female patients. Even with the additional condition of "older age," perhaps the COVID-19 was not yet severe at admission, and there was adequate time after admission to discuss the treatment plan, including IMV, with healthcare providers. In addition, "older, non-obese, and female" patients comprise the majority of residents in long-term nursing care facilities. In Japan, older people with advanced frailty and reduced oral intake are often thin, and women tend to have a longer life expectancy (21). These women may have discussed their end-oflife treatment plans with family members and facility staff in advance and may have expressed their intentions in writing. For example, although not in the COVID-19

era, a previous study found that the rate of advance directives was high among nursing home residents and hospice users aged  $\geq$  65 years (22) and more women than men provided do not attempt resuscitation instructions (23,24). In the present study, patients may have heard news reports about the situation and treatment options in the COVID-19 pandemic, considered which treatment options they would like, and indicated some preferences for medical measures after hospitalization, either in advance or at admission. Three, in older patients, even if respiratory failure is not caused by COVID-19, patients may die because of exacerbation of the underlying disease or complications triggered by COVID-19 (25). It is possible that there were cases in which the underlying disease worsened or complications developed after admission, and IMV was not indicated in these cases.

Fourth, the participants of this study were patients in the first through fourth waves of COVID-19. During this period, the capacity to accept patients with severe COVID-19 was always greater than the actual number of patients with COVID-19 on ventilators nationwide (26). There was no obvious depletion of medical equipment, such as ventilators (21,22), nor reports that the capacity of intensive care was exceeded. Of note, there was fair allocation of medical resources at the macro, meso, and micro levels (27), with no reports suggesting otherwise. Thus, the principle of justice may be irrelevant to the results of this study.

However, although the number of beds notified to the government was secured, the actual supply-demand balance was tight, as requests were not easily met in the medical wards and intensive care units (28). For example, many deaths occurred in Japan for the first time in the fourth wave (29), which may reflect resource constraints in medical facilities. Therefore, whether access to ventilators was sufficient during the extreme phase of the COVID-19 pandemic should be further considered.

Our study has several limitations. First, we lacked data on the presence or absence of advance care planning (ACP) prior to infection, the decision-making process at admission, and the patients' own wishes. Therefore, we could not examine whether patients received the care they wanted (goal-concordant care) and the decisionmaking regarding ACP immediately after admission.

Second, we only included patient factors as explanatory variables, and withholding life-sustaining treatments involves a complex set of factors, including factors related to the healthcare provider and medical institution. Future research should include these factors as explanatory variables.

Third, we could not identify the reasons for withholding IMV in this study; we could not evaluate every unique patient scenario with the ethical considerations. Future research should explore the reasons for withholding IMV in each patient.

Fourth, we did not assess frailty scores in this

study. Frailty and older age have been reported to be the greatest predictors of COVID-19 mortality (30). Given that IMV tended to be withheld in women with non-obese status, frailty may be a confounding factor. Therefore, further studies are warranted.

Fifth, patients with COVID-19, especially the older patients, die from exacerbation of the original underlying disease or complications triggered by COVID-19. Especially after the omicron strain, most patients died of exacerbation of the original underlying disease or complications, whereas patients infected with the delta strain died of respiratory failure due to COVID-19 pneumonia (25). In this study, we focused on patients from the first through fourth waves (alpha strain was dominant), and most patients died of respiratory failure due to COVID-19 pneumonia.

Finally, although this study included a large number of COVID-19 inpatients in Japan, there may have been some selection bias for inclusion, as noted above, and due to the manual input of the data. Thus, the study results may not accurately reflect the actual status of the general Japanese population hospitalized for COVID-19 (*1*).

In conclusion, we explored patient factors and data associated with the withholding of IMV and analyzed the results based on the four principles of biomedical ethics by taking a retrospective look at the treatment decision-making process in the COVID-19 disaster and considering multidisciplinary collaboration, including palliative care teams. This study indicates that none of the results significantly diverged from the four principles, although this alignment may be coincidental. Building on these findings, we recommend that future pandemic preparedness efforts incorporate a systematic, preemptive evaluation of decision-making concerning life-sustaining interventions — such as IMV — from both scientific and ethical perspectives, including the four principles of biomedical ethics.

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## The frequency of peripheral blood eosinophilia and its clinical significance in patients with dermatomyositis

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Abstract: In connective tissue diseases, eosinophil is thought to varying extents to be involved in the pathogenesis. Increased eosinophils in the skin tissues of patients with dermatomyositis (DM) have been reported, but there have been no investigations of blood eosinophilia in patients with DM. This study is the aim of determining the frequency of peripheral blood eosinophilia and elucidating its clinical significance. We retrospectively collected the clinical records of 48 patients (15 men and 35 women) who were diagnosed with classical DM (n = 34), ADM (n = 13), and JDM (n = 1), on the basis of the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies. Eosinophil count  $\geq 400/\text{mm}^3$  was observed in 14.6% (n = 7) of the patients, while 4.2% (n = 2) of patients had eosinophil counts >1,000/mm<sup>3</sup>. Regarding the clinical significance of peripheral blood eosinophilia in DM patients, in seven patients with increased blood eosinophil counts, the prevalence of Gottron's sign/papules, heliotrope rash, V-neck sign, shawl sign, pruritus, internal malignancy, and positive anti-TIF1- $\gamma$ antibody were more frequent than in those without (85.7%, 85.7%, 71.4%, 71.4%, 85.7%, 42.9%, 28.6% vs. 92.7% p = 0.48, 61.0% p = 0.40, 36.6% p = 0.11, 39.0% p = 0.22, 36.6% p = 0.034, 19.5% p = 0.33, and 19.5% p = 0.63,respectively). Among them, pruritus was more common in patients with elevated eosinophil counts with statistical significance. The activity of eosinophilia and severity of skin eruptions also tended to be correlated. In summary, our study suggests that blood eosinophilia is correlated with the presence of pruritus, but not disease-associated autoantibodies or internal malignancy.

Keywords: dermatomyositis, eosinophilia, peripheral blood, pruritus, rash

#### Introduction

Idiopathic inflammatory myopathies are heterogeneous autoimmune disorders that include polymyositis, dermatomyositis (DM) and inclusion body myositis (1). Among them, the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for adult and juvenile idiopathic inflammatory myopathies distinguished between classical DM, amyopathic DM (ADM) and juvenile DM (JDM).

As representative skin manifestations of DM, heliotrope rash and Gottron's sign/papules are included in the diagnostic criteria, and they are thought to be induced by chronic physiological stimuli (2). V-neck sign and shawl sign may be induced by the photosensitivity characteristic of this disease. In addition, vasculopathy including skin ulcers is also seen in DM, especially in patients with anti-melanoma differentiation-associated gene 5 (MDA5) antibody (3). These skin eruptions are often accompanied by pruritus, which is more common in patients that are positive for anti-transcriptional intermediary factor (TIF)  $1-\gamma$  antibody (4).

Eosinophils have diverse roles in human diseases. They express various pattern recognition receptors, including toll-like receptors, nucleotide-binding oligomerization domain-like receptors, and G proteincoupled, Fc, chemokine, adhesion, and cytokine receptors (5). Stimulation of these receptors induces degranulation of toxic granule proteins such as eosinophil peroxidase, eosinophil cationic protein, eosinophil-derived neurotoxin, and major basic protein. Synthesis of nitric oxide, the release of cytokines or chemokines, and cell trafficking are also activated. Through these processes, eosinophils contribute to host defense as innate immune cells. In connective tissue diseases, eosinophil is thought to varying extents to be involved in their pathogenesis. For example, eosinophils play significant roles in the pathogenesis of systemic vasculitis such as eosinophilic granulomatosis with polyangiitis or eosinophilic fasciitis.

On the other hand, peripheral blood eosinophilia can be primary or secondary, and most cases are secondary (e.g., drug, bronchial asthma, atopic dermatitis, parasitic infections, malignant tumors, and autoimmune diseases). Among autoimmune diseases, several studies have focused upon blood eosinophilia in primary biliary chlangitis, found in more than 50% of patients (6). Eosinophilia in rheumatoid arthritis (RA) has been reported, and the frequency of eosinophilia in Argentinian patients with RA was 7% (7). In the peripheral blood of patients with systemic sclerosis (SSc), an eosinophil count of  $> 300/\text{mm}^3$  or  $> 1,000 \text{ mm}^3$  can be seen in 16% or 1% of patients, respectively (8,9). We previously analyzed the correlation between vascular abnormalities and peripheral blood eosinophils in SSc patients; the timing of the emergence of the maximum blood eosinophil counts was related to ulcer development (10).

There can also be increased eosinophils in the skin tissues of patients with DM (11). However, there has not yet been a proper investigation of blood eosinophilia in DM patients. In the present study, we performed a retrospective analysis to determine the frequency of peripheral blood eosinophilia and to elucidate its clinical significance in DM patients.

#### **Patients and Methods**

#### Patient material and clinical assessment

This study was conducted in 2022 by retrospectively collecting the clinical records of 48 patients (15 men and 35 women) who were diagnosed with classical DM (n = 34), ADM (n = 13), and JDM (n = 1), on the basis of the 2017 EULAR/ACR classification criteria for adult and juvenile idiopathic inflammatory myopathies between 2009 and 2021 (1).

We excluded patients who lacked laboratory data, whose treatment (*e.g.*, immunosuppressive agents, glucocorticoids) had already been initiated, who already administrated anti-histamine drugs, who were accompanied by hematopoietic disorders, and who had complications that may alter peripheral blood eosinophil number (*e.g.*, allergic disorders).

Clinical and laboratory data were obtained at the time of the first visit to our hospital (Table 1). The average age of patients or duration of disease was  $57.0 \pm 16.2$  years or  $7.0 \pm 12.8$  months, respectively. Antinuclear antibodies (ANA) were detected by indirect immunofluorescence using HEp-2 cells as the substrate. Also, dermatomyositis-specific autoantibodies were examined by enzyme-linked immunosorbent assay (ELISA) or immunoprecipitation (IP) assay. The presence of clinical features including pruritus was determined by the description in medical records. Pruritus due to skin rash of dermatomyositis was focused, and those due to

other diseases (*e.g.* urticaria) or drug-induced itchiness were excluded.

This study was approved by the Wakayama Medical University Institutional Review Board (No.3423) and written informed consents were obtained before patients were entered into this study, which was conducted in accordance with the Declaration of Helsinki.

#### Statistical analysis

Statistical analysis was assessed by Mann-Whitney U-test or Fisher's exact probability test for comparison of medians or percentages, respectively. Correlations were evaluated by Pearson's correlation. P values < 0.05 were considered to be statistically significant.

#### **Results and Discussion**

#### Clinical features of patients in this study

Forty-eight patients with classical DM (n = 34), ADM (n = 13), and JDM (n = 1) were retrospectively collected in this study. The clinical characteristics of patients

Table 1. Summary of clinical/serological features in patients with dermatomyositis (DM, n = 48)

Features	Values	
Age at the first visit (mean years $\pm$ SD)	57.0 ± 16.2	
Duration of disease (mean months $\pm$ SD)	$7.0 \pm 12.8$	
Type (classical DM:ADM:JDM)	34:13:1	
CLINICAL FEATURES		
Gottron's sign/papules (%)	91.7	
Heliotrope rash (%)	64.6	
V-neck sign (%)	41.7	
Shawl sign (%)	43.8	
Pruritus (%)	43.8	
Internal malignancy (%)	22.9	
LABORATORY FEATURES		
CK (U/L)	$1,302 \pm 2,740.8$	
AST (U/L)	$122.2\pm130.9$	
ALT (U/L)	$72.8\pm71.7$	
LDH (U/L)	$454.6 \pm 235.1$	
ANA (> ×80)	37.5	
anti-ARS antibody (%)	10.4	
anti-MDA5antibody (%)	41.7	
anti-TIF1-γ antibody (%)	20.8	
anti-Mi2 antibody (%)	2.1	
anti-NXP2 antibody (%)	2.1	
Others (%)	22.9	
ORGAN INVOLVEMENT		
Muscle (%)	70.8	
Lung (%)	64.6	
Dysphasia (%)	20.8	
Joint (%)	35.4	

Unless indicated, values are average  $\pm$  standard deviation. DM, dermatomyositis; ADM, amyopathic dermatomyositis; JDM, juvenile dermatomyositis; CK, creatin kinase; ANA, antinuclear antibody; ARS, aminoacyl-tRNA synthetase antibody; MDA5, melanoma differentiation-associated gene 5 antibody; TIF1- $\gamma$ , transcriptional intermediary factor 1- $\gamma$  antibody; NXP-2, nuclear matrix protein. \*p < 0.05, versus patients with normal blood eosinophil counts using Fisher test.

included in this study are shown in Table 1. As a result, the prevalence of patients with Gottron's sign/papules, heliotrope rash, V-neck sign, shawl sign, pruritus, and internal malignancy were 91.7%, 64.6%, 41.7%, 43.8%, 43.8%, and 22.9%, respectively. About 50% of patients with DM reportedly have moderate to severe pruritus, which is consistent with the present study (*12*).

Regarding autoantibodies associated with DM, the positivity of anti-aminoacyl-tRNA synthetase (ARS) antibody, anti-MDA5 antibody, anti-TIF1- $\gamma$  antibody, anti-Mi2 antibody, and anti-nuclear matrix protein (NXP-2) antibody were 10.4%, 41.7%, 20.8%, 2.1%, and 2.1%, respectively. The most common organ involvement was skeletal muscle myopathy (70.8%), followed by interstitial lung disease (64.6%).

#### Correlation between serum eosinophil counts and clinical/serological features in patients with DM

In patients included in the present study (n = 48), blood eosinophil counts were 0-1,013/µl (average ± standard deviation = 184.7 ± 252.6/µl), whereas eosinophil percentages were 0-20% (2.93 ± 3.64%). Eosinophil count ≥ 400/mm<sup>3</sup> was observed in 14.6% (n = 7) of the patients, whereas 4.2% (n = 2) of patients showed eosinophil counts > 1,000/mm<sup>3</sup>.

We examined the correlation of blood eosinophil counts with clinical and serological features in patients with classical DM/ADM/JDM (Table 2). If eosinophil count  $\geq 400 / \mu l$  is defined as a significant increase, in seven patients with increased blood eosinophil counts, the frequency of Gottron's sign/papules (85.7%) was comparable with that in the patients with normal eosinophil counts (92.7%). In contrast, the prevalence of heliotrope rash, V-neck sign, shawl sign, pruritus, and internal malignancy were more frequent in patients with increased blood eosinophil counts (85.7%, 71.4%, 71.4%, 85.7% and 42.9% vs. 61.0%, 36.6%, 39.0%, 36.6%, and 19.5%, respectively). Among them, only the difference in frequency of pruritis was statistically significant (p = 0.034 by Fisher's exact probability test).

As for muscle involvement, levels of creatin kinase were not significantly higher in patients with elevated eosinophil counts than in those with normal eosinophil counts (1,732.9  $\pm$  1,704.3 vs. 1,228.4  $\pm$  2,874.3 U/L). Among disease-associated autoantibodies, the percentage of anti-MDA5 antibody was slightly lower and anti-TIF1- $\gamma$  antibody higher in patients with increased blood

Table 2. Correlation of blood eosinophil levels with clinical/serological features in patients with dermatomyositis (DM, n = 48)

Features	Blood eosin		
	Patients with elevated ( $\geq 400/\mu$ L) eosinophil counts ( <i>n</i> = 7)	Patients with normal ( $< 400/\mu$ L) eosinophil counts ( $n = 41$ )	<i>p</i> value
Age at the first visit (mean years $\pm$ SD)	$59.0\pm10.1$	$57.0\pm16.8$	
Duration of disease (mean months $\pm$ SD)	$9.0 \pm 16.1$	$6.0 \pm 12.1$	
Type (DM:ADM:JDM)	6:1:0	28:12:1	
CLINICAL FEATURES			
Gottron's sign/papules (%)	85.7	92.7	0.48
Heliotrope rash (%)	85.7	61.0	0.40
V-neck sign (%)	71.4	36.6	0.11
Shawl sign (%)	71.4	39.0	0.22
Pruritus (%)	85.7*	36.6	0.03
Internal malignancy (%)	42.9	19.5	0.33
LABORATORY FEATURES			
CK (U/L)	$1732.9 \pm 1704.3$	$1228.4 \pm 2874.3$	0.25
AST (U/L)	$170.0 \pm 156.4$	$114.0 \pm 124.2$	0.41
ALT (UL)	$116.3 \pm 124.7$	$65.4 \pm 55.4$	0.40
LDH (U/L)	$519.6 \pm 149.4$	$443.5 \pm 245.1$	0.12
ANA (> ×80)	71.4	28.6	0.09
anti-ARS antibody (%)	14.3	9.8	0.56
anti-MDA5antibody (%)	14.3	46.3	0.21
anti-TIF1-γ antibody (%)	28.6	19.5	0.63
anti-Mi2 antibody (%)	0	2.4	1.00
anti-NXP2 antibody (%)	14.3	0	0.15
Others (%)	28.6	22.0	0.65
ORGAN INVOLVEMENT			
Muscle (%)	85.7	68.3	0.66
Lung (%)	42.9	68.3	0.23
Dysphasia (%)	28.6	19.5	0.63
Joint (%)	14.3	39.0	0.40

Unless indicated, values are average±standard deviation. DM, dermatomyositis; ADM, amyopathic dermatomyositis; JDM, juvenile dermatomyositis; CK, creatin kinase; ANA, antinuclear antibody; ARS, aminoacyl-tRNA synthetase antibody; MDA5, melanoma differentiation-associated gene 5 antibody; TIF1- $\gamma$ , transcriptional intermediary factor 1- $\gamma$  antibody; NXP-2, nuclear matrix protein. \*p < 0.05, versus patients with normal blood eosinophil counts using Fisher test.

eosinophil counts compared with those with normal eosinophil counts (14.3 and 28.6% *vs.* 46.3 and 19.5%, respectively).

DM patients with anti-TIF1- $\gamma$  antibody or internal malignancy have been thought to be correlated with pruritic skin rash (13,14). However, in this study, the percentage of internal malignancy and positive anti-TIF1- $\gamma$  antibody was slightly elevated in patients with increased blood eosinophil counts, but without statistically significant difference. Taken together, our study suggests that blood eosinophilia is correlated with the presence of pruritus, but not disease-associated autoantibodies or internal malignancy.

## *Clinical course and images of patients with increased blood eosinophil counts*

Among the seven patients with increased blood eosinophil counts, the clinical courses of five patients were recorded (Figure 1). According to longitudinal data, the timing of emerging the increased eosinophil counts tended to be similar to that of the skin eruptions, before and after the treatment with glucocorticoid and/or immunosuppressive agents.



Figure 1. The clinical course of five patients with increased peripheral blood eosinophilia. CK, creatine kinase; PSL, prednisolone; DXS, dexamethasone; BMS, betamethasone; mPSL, methyl-prednisolone; CyA, Cyclosporin A; TAC, tacrolimus; IVCY, intravenous cyclophosphamide. Solid lines; serum CK levels, dotted lines; eosinophil counts. The severity of skin rash is indicated by the red graph.

A representative clinical picture of one of the seven patients with increased eosinophils (case A in Figure 1) is shown in Figure 2. The classical DM patient was positive for anti-NXP2 antibody, and skin manifestations included shawl sign, Gottron's sign, and periungual erythema. Blood eosinophil counts and CK levels at the initial visit were 459/µl (7.0%) and 1,287 U/l. The treatment with glucocorticoids rapidly reduced CK levels, blood eosinophil counts, and severity of skin eruption.

Our study indicated that there tends to be correlation between activity of eosinophilia and severity of skin eruptions in DM patients. We previously demonstrated that the timing of emerging of the maximum eosinophil counts was correlated with the ulcer development in SSc, and suggested the possibility that eosinophils may be involved in the pathogenesis of vascular dysfunction (10).

Eosinophils have reportedly been found in 10-20% of biopsies of DM skin lesions (*11,15,16*). Actually, eosinophils are one of the sources of IL-31, a cytokine that bridges inflammation and pruritus (*17*). Expression of IL-31 and IL-31 receptors in DM skin lesions were reported to be up-regulated compared with normal skin (*12*). Accordingly, eosinophils in the skin may be involved in the cause of pruritus in patients with DM. However, although skin biopsy specimen was available



Figure 2. Clinical pictures of anti-NXP2 antibody-positive patients with classical DM (with clinical course shown in Figure 1A). (A) Shawl sign on the upper back and erythema on the lumbar region before treatment; (B) Erythema on the thighs and Gottron's sign on the knees before treatment; (C) Periungual erythema before treatment; (D) Eruption of the upper back and lumbar region after treatment on day 100; (E) Eruption of the thighs and knees after treatment on day 100.

in five out of the seven patients with increased blood eosinophil counts, eosinophil infiltration in the dermis was not found in the five patients histopathologically. Thus, we could not prove the association between peripheral blood eosinophilia and eosinophil infiltration in skin tissue. Notably, Kumamoto *et al.* reported that eight out of 680 muscle biopsies of polymyositis patients were identified with > 0.3 eosinophils/mm<sup>3</sup> in the inflammatory infiltrate without concomitant peripheral eosinophilia (*18*). These patients tended to show a marked elevation of serum creatine kinase. Therefore, eosinophil infiltration in each tissue and peripheral blood is unlikely to correlate directly.

This is a pilot study with a small number of samples. To obtain more accurate and reliable data, a larger number of samples are necessary in future studies.

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## Paraganglioma of the spermatic cord: A rare tumor with unique imaging findings and diagnostic challenges

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Abstract: Pheochromocytomas and paragangliomas are rare endocrine neoplasms derived from neural crest cells, with spermatic cord paragangliomas being exceptionally uncommon. A 42-year-old man presented with a longstanding complaint of left scrotal enlargement. Initial imaging raised suspicion of testicular carcinoma, but contrast-enhanced computed tomography and magnetic resonance imaging revealed a well-circumscribed, hypervascular mass distinct from the testis. The tumor exhibited heterogeneous T2 signal intensity, characteristic of vascular lesions, a thick capsule, and early-phase peripheral contrast enhancement with delayed homogeneous filling. A solitary fibrous tumor was initially considered as a differential diagnosis. Surgical resection confirmed the tumor's origin in the spermatic cord. Histopathology revealed small, round neoplastic cells with a delicate sinusoidal vascular network, and immunohistochemical analysis was positive for chromogranin A and synaptophysin, confirming the diagnosis of paraganglioma, with its origin traced to the spermatic cord. The surgical margins were clear, and postoperative imaging showed no metastases. At 18 months follow-up, no recurrence was detected, and biochemical markers remained normal. This case highlights the diagnostic challenges of spermatic cord paragangliomas due to their rarity and imaging resemblance to other intra-scrotal neoplasms. Although preoperative diagnosis is crucial for appropriate management, almost all of the reported cases of spermatic cord paragangliomas have been diagnosed postoperatively. New imaging techniques, including <sup>68</sup>Ga-DOTATATE PET/CT, may change this situation. This report expands the limited literature on spermatic cord paragangliomas and underscores the importance of considering paraganglioma in the differential diagnosis of intra-scrotal masses.

Keywords: pheochromocytoma, scrotum, urogenital system

#### Introduction

Pheochromocytomas and paragangliomas (PPGLs) are endocrine neoplasms that originate from the chromaffin cells of the adrenal medulla or from the chromaffin-like cells located within the sympathetic or parasympathetic paraganglia, all of which derive from the neural crest. PPGLs are among the most genetically predisposed tumors, with more than twenty susceptibility genes identified to date, contributing to germline mutations in about 40% of cases (1,2). Prominent among the syndromes associated with PPGLs are Von Hippel-Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1. The emergence of paragangliomas within the genitourinary tract, particularly those originating in the spermatic cord, is exceedingly rare. Herein, we present a case of a paraganglioma arising in the spermatic cord and contribute to the knowledge regarding these uncommon neoplasms. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient.

#### **Case Report**

A 42-year-old man was referred to our institution in May 2023 for evaluation of a progressive enlargement of the left scrotum which he had observed for several years but had hitherto neglected. At another facility, a presumptive diagnosis of left testicular carcinoma was considered. The patient's medical history was otherwise unremarkable, with no evidence of hypertension or tachycardia. Physical examination revealed a palpable, elastic, hard mass approximately 5 cm in diameter within the left scrotum. Serum levels of alpha-fetoprotein and human chorionic gonadotropin were within normal parameters. Radiological assessment *via* abdominal contrast-enhanced computed tomography revealed a neoplasm measuring 6 cm in diameter, characterized by heterogeneous hypoattenuation and the presence of multiple venous proliferations surrounding the lesion (Figure 1A).

Contrast-enhanced magnetic resonance imaging demonstrated a scrotal mass with a diameter of 6 cm, featuring a relatively thick capsule exhibiting low signal intensity and a heterogeneous high signal intensity interior on T2-weighted sequences (Figure 1B) and dispersed high-signal foci within the mass on T1weighted sequences. Serpentine dilated arterioles were observed proximal to the neoplasm, exhibiting rapid contrast enhancement from the periphery during the early phase. In the delayed phase, the enhancement appeared relatively homogeneous extending to the interior of the mass (Figures 1C and D). A solitary fibrous tumor, likely originating from the peritoneal sheath, was considered as a differential diagnosis. The mass was discerned to be anatomically distinct from the testis.

The intra-scrotal mass was surgically resected. Intraoperative observations confirmed the tumor's origin from the spermatic cord, necessitating the ligation and transection of the cord more than 2 cm proximal to the lesion due to the impracticality of testicular preservation. No perioperative complications, such as blood pressure fluctuations or tachycardia, were encountered, and the patient recovered uneventfully. Macroscopically, the specimen revealed a substantial neoplasm measuring 50 x 45 x 35 mm on the cut surface. The lesion exhibited a yellowish-white color, interspersed with internal hemorrhage (Figure 2A). Microscopic examination identified relatively small neoplastic cells proliferating in a focal arrangement, set against a backdrop of a delicate sinusoidal vascular network. These tumor cells exhibited small, round nuclei and relatively abundant pale cytoplasm (Figure 2B).

Immunohistochemical staining demonstrated positivity for chromogranin A and synaptophysin and negativity for anti-epithelial antigen 1/anti-epithelial antigen 3 (Figure 2C and D). These findings led to the diagnosis of a paraganglioma of the spermatic cord. The surgical margins were free of tumor involvement.

Postoperative evaluation *via* 18F-fluorodeoxyglucose positron emission tomography revealed no evidence of distant metastases, confirming the localized nature of the neoplasm. At 18 months postoperatively, computed tomography revealed no evident metastatic recurrence, and plasma-free metanephrines and normetanephrines remained within normal limits.

#### Discussion

PPGLs are rare endocrine tumors arising from adrenal medulla or paraganglia cells, associated with a risk of metastasis. The latest guidelines and World Health Organization classification emphasize that all PPGLs have metastatic potential and define malignancy as the presence of metastases in non-chromaffin cell locations (3). Risk assessment for metastasis involves considering tumor size, location, the presence of a



Figure 1. (A) Contrast-enhanced CT shows a 6 cm neoplasm with heterogeneous hypoattenuation and surrounding venous proliferations; (B) T2-weighed magnetic resonance image shows a scrotal mass with a thick capsule of low signal and a heterogeneous, high-signal interior (black arrowhead). The left testis is denoted by a white arrowhead; (C) The post-contrast dynamic study revealed a prominently dilated feeding artery and drainage veins, accompanied by rapid intratumoral enhancement starting from the periphery; (D) Fast field echo resembling a computed tomography scan using restricted echo-spacing.



Figure 2. Pathological findings. (A) The tumor exhibits with a yellowish-white color, accompanied by mixed patterns of internal hemorrhage; (B) Microscopic image reveals small neoplastic cells in focal arrangements, amid a fine sinusoidal vascular network, with these cells displaying small, round nuclei and abundant pale cytoplasm; (C) Immunohistochemical examination reveals positive staining for chromogranin A; (D) Immunohistochemical examination reveals positive staining for synaptophysin.

succinate dehydrogenase subunit B (SDHB) mutation, dopaminergic phenotype, and the Ki-67 index (1,2,4). Immunohistochemistry for SDHB and metabolite profiling are crucial for identifying SDHB mutations and assessing metastatic risk, although genetic testing remains essential for accurate diagnosis (5).

The Pheochromocytoma of the Adrenal Gland Score and the Grading of Adrenal Pheochromocytoma and Paraganglioma score are the primary histological tools for risk stratification, indicating potential malignant behavior with varying sensitivity and specificity (6,7). Studies suggest that 10% to 15% of pheochromocytomas and 35% to 40% of paragangliomas develop metastases, with a reported median overall survival of 7 years for metastatic cases (2,8,9).

PPGLs are the most heritable tumor types. Considering the spectrum of known germline mutations, approximately 30% to 35% of patients with PPGL harbor germline mutations in various susceptibility genes, while an additional 35% to 40% possess somatic driver mutations (10). Collectively, approximately 70% of PPGL cases exhibit mutations in more than 20 identified PPGL driver genes, categorized into three principal molecular clusters: pseudohypoxia cluster 1, kinase-signaling cluster 2, and Wnt signaling cluster 3. This categorization correlates with distinct biochemical phenotypes, clinical courses, and prognostic outlooks. Moreover, genetic abnormalities affecting telomere and chromatin maintenance are implicated in further influencing the disease trajectory (10-12).

All patients with a history of PPGL and asymptomatic mutation carriers require lifelong follow-up tailored to their mutation status and disease characteristics. Surgical removal is the primary treatment, with chemotherapy, radionuclide therapy, and tyrosine kinase inhibitors as options for inoperable or metastatic disease (1,2). Future treatment strategies may include genetically driven, cluster-specific therapies, though these are not yet standard practice.

Given the rarity of paragangliomas, estimating their prevalence, particularly in the genitourinary tract, presents significant challenges. These neoplasms have been identified in various genitourinary locations, including the kidney and renal pelvis, ureters, urethra, prostate gland, and notably, the bladder, which is the most common site of occurrence (13). A retrospective observational analysis of the Surveillance, Epidemiology, and End Results database identified 299 instances of paragangliomas, of which 20 (6.7%) originated from the genitourinary tract. Among these, the majority occurred in the bladder (83%), followed by the kidney and renal pelvis (17%), with a minor proportion arising from the spermatic cord (2%) (13). A literature search was conducted using PubMed, Embase, and Google Scholar to identify previously reported cases of spermatic cord paraganglioma. This case represents the eighteenth reported instance of a paraganglioma in the spermatic cord in medical literature, thereby expanding our understanding of such rare occurrences. Due to the lack of distinct imaging characteristics, almost all cases of spermatic cord paraganglioma are diagnosed intraoperatively through frozen section analysis or postoperatively. However, a recent report described a case of spermatic cord paraganglioma in which a preoperative diagnosis was successfully made using <sup>68</sup>Ga-DOTATATE PET/CT (14). This was possible because PPGLs overexpress somatostatin receptors, and recent studies have demonstrated the excellent utility of <sup>68</sup>Ga-DOTATATE PET/CT in localizing both primary and metastatic PPGLs (*15*).

In conclusion, this report details a case of an uncommon paraganglioma associated with spermatogenic tissue. It underscores the necessity of considering paraganglioma in the differential diagnosis of challenging intra-scrotal neoplasms.

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# A fatal case of pyogenic spondylitis rapidly progressing to epidural abscess caused by a novel ST-type methicillin-susceptible *Staphylococcus aureus* ST9378

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**Abstract:** Pyogenic spondylitis can be life-threatening; however, its diagnosis remains challenging because of the initial presentation of nonspecific symptoms. Given the vulnerability of the infected site, patients are highly at risk for severe complications, such as epidural abscesses or bacterial meningitis, which can considerably worsen the prognosis. Herein, we report a case of lumbar pyogenic spondylitis initially identified through methicillin-susceptible *Staphylococcus aureus* bacteremia, which subsequently progressed to an epidural abscess. The abscess rapidly ascended to the cervical region, causing bacterial meningitis and ultimately, a fatal outcome. The strain (JARB-OU3818) was positive for the virulence factor genes of the enterotoxin gene cluster (*seg, sei, sem, sen, and seo*) but negative for the Panton-Valentine leucocidin (PVL) and toxic shock syndrome toxin-1 (TSST-1) coding genes. Additionally, JARB-OU3818 was ST9378 belonging to the clonal complex 45 lineage. Clinicians should recognize that pyogenic spondylitis may follow an aggressively progressive clinical course, as demonstrated by this case.

Keywords: pyogenic spondylitis, epidural abscess, Staphylococcus aureus

#### Introduction

Pyogenic spondylitis is an infection associated with a relatively high mortality rate of 5%-13% among inpatients (1-5). The onset-to-diagnosis period for hematogenous pyogenic spondylitis varies from several days to several weeks (6). Cases caused by gramnegative bacilli are generally acute, whereas those caused by gram-positive cocci are often chronic (7). Hematogenous cases typically begin with nonspecific symptoms (7), such as fever and joint pain, delaying the diagnosis and appropriate treatment.

Various bacteria can act as causative pathogens in pyogenic spondylitis, with *Staphylococcus aureus* being notably common, especially in hematogenous cases (6). *S. aureus* can also cause abscess formation; in pyogenic spondylitis, complications such as epidural abscesses, psoas muscle abscesses, and sometimes, bacterial meningitis may develop. Of note, when pyogenic spondylitis develops into bacterial meningitis, the mortality rate significantly increases (8).

Herein, we report a case of lumbar pyogenic

spondylitis caused by methicillin-sensitive *S. aureus*, progressing rapidly with complications such as epidural abscess and meningitis and ultimately, a fatal outcome, in a 77-year-old man. Multilocus sequence typing (MLST) analysis of the strain revealed a novel sequence type. Informed consent to publish this paper was obtained from his family. This case report was conducted in accordance with the ethical principles of the Declaration of Helsinki.

#### **Case Report**

A 77-year-old man with diabetes history visited our emergency department complaining of worsening pain in his right lower leg over 10 days. He twisted his foot while working as a plasterer 12 days prior, leading to persistent right thigh pain. After 6 days, given the lack of improvement, he visited an orthopedic clinic, where an X-ray revealed no bone abnormalities; thus, he was merely prescribed with a nonsteroidal anti-inflammatory drug (NSAID). However, the pain worsened, prompting a visit to our emergency department 2 days before

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admission. Initial blood tests revealed elevated inflammatory markers, including a white blood cell count of 11,800/mm<sup>3</sup> and a C-reactive protein (CRP) level of 25.6 mg/dL. Chest and abdominal computed tomography (CT) scans showed no apparent fever source and no evident bone lysis or fractures. Blood cultures were taken, and the patient returned home. On admission day, blood cultures turned out to be positive for gram-positive cocci (in 2 of 2 sets); hence, he was hospitalized for further treatment. Upon admission, physical examination showed no signs of conjunctival hemorrhage, abnormal heart, or lung sounds, but he had spontaneous pain extending from the lumbar region to the right thigh, with marked percussion tenderness around the sacral area. Laboratory results showed elevated inflammatory markers (CRP: 32.38 mg/dL), renal impairment (blood urea nitrogen, 49.7 mg/dL; serum creatinine 1.74 mg/ dL), and hyperglycemia (HbA1c, 7.7%).

Following the detection of gram-positive cocci in blood cultures, empirical vancomycin therapy was initiated. On day 1, the organism was identified as methicillin-susceptible S. aureus; thus, the drug was switched to cefazolin. Magnetic resonance imaging (MRI) of the lumbar spine performed on day 2 revealed high-intensity T2- and diffusion-weighted imaging signs from thoracic (Th)6 to lumbar (L)5, indicating an epidural abscess, as well as vertebral osteomyelitis at L5 (Figure 1A). Nonetheless, neurological findings remained unremarkable. Therefore, conservative management without surgical drainage was chosen. However, on day 4, he developed upper limb tremors. Subsequent MRI of the head and neck revealed that the epidural abscess extended from Th5 to cervical (C)1 (Figure 1B). Therefore, the orthopedic surgeons deemed surgical intervention inappropriate. Lumbar puncture revealed cerebrospinal fluid (CSF) findings (cell count, 1,173/ $\mu$ L; glucose level, 21 mg/dL [versus blood glucose level of 231 mg/dL]) suggestive of bacterial meningitis. Hence, ceftriaxone was initiated, leading to gradual improvement in inflammatory markers (CRP, 15.31 mg/ dL; CSF cell count, 483/ $\mu$ L by day 11). Unfortunately, the patient developed consciousness disturbance (Japan coma scale, III-100) on day 13 and passed away on day 14.

Pathological autopsy revealed an enlarged right iliopsoas muscle with a bloody purulent discharge upon incision (Figure 2A). An abscess adhered to the dorsal meninges at the foramen magnum, with numerous granular white spots on the arachnoid internal surface (Figure 2B, 2C). Histologically, the iliopsoas abscess had inflammatory cell infiltration and hemosiderin deposition. Extensive inflammatory cell infiltration was also observed along the dura mater, extending from the lumbar spine to the cervical spine and brainstem, including the medulla, pons, and cerebellum surfaces. Of all the various sites examined by culture, only the right iliopsoas region exhibited S. aureus growth. This strain was named JARB-OU3818. Table 1 lists the susceptibility test results for this strain. Meanwhile, the heart valves and other organs had no abscess formation.

We investigated the genotype of JARB-OU3818 by whole-genome analysis, following previously described methods (9). The sequence type (ST) of JARB-OU3818 was defined using mlst v2.22.1 (*https://github.com/ tseemann/mlst*), which extracts seven housekeeping genes (*arcC*, *aroE*, *glpF*, *gmk*, *pta*, *tpi*, and *yqiL*) from the whole-genome sequence of this strain and matches them against characterized ST number in the *S. aureus* 



Figure 1. (A) DWI image of lumbar spine. High signal in L5 vertebral body suggested osteomyelitis, and high density area in Th6 to L5 suggested epidural abscess. (B) DWI image of cervical spine. High density area in C1 to Th5 suggested epidural abscess.

(A)

**(B)** 



Figure 2. (A) Incision finding in right iliopsoas muscle. Bloody purulent fluid was discharged. (B) Foramen magnum finding. An abscess adhered to the dorsal meninges. (C) Head finding. Numerous granular white spots were found on the arachnoid surface.

PubMLST database (https://pubmlst.org.organisms/ staphylococcus-aureus/). As a result of the search, no ST numbers were found in the PubMLST database that matched the allele numbers of the seven genes (arcC, 10; aroE, 14; glpF, 8; gmk, 6; pta, 1102; tpi, 3; and yqiL, 2) of JARB-OU3818. Therefore, these seven allele numbers of JARB-OU3818 were registered as a new ST9378. The raw read sequence data have been deposited in the DDBJ Sequence Read Archive under the accession number DRR628060. We found that JARB-OU3818 had no mecA, the methicillin resistance gene, and any other antimicrobial resistance genes. However, it contained virulence-factor-related genes such as the coagulase type VIIb gene and the enterotoxin gene cluster (egc; seg, sei, sem, sen, and seo), while Panton-Valentine leukocidin (PVL) and toxic shock syndrome toxin 1 (TSST-1) genes were not detected. JARB-OU3818 was classified as a new ST9378 type by MLST analysis and as clonal complex 45 by eBURST analysis.

#### Discussion

Pyogenic spondylitis remains to be highly fatal, with recent in-hospital mortality rates ranging between 5% and 13% (1-5). Its diagnosis is often delayed because of the nonspecificity of its initial symptoms, such as fever and back pain. In some cases, the absence of fever makes an early diagnosis even more challenging

Table 1. Susceptibility test results of JARB-OU3818

Antibiotics	MIC (µg/mL)	Interpretation
penicillin G	0.06	S
oxacillin	$\leq 0.25$	S
sulbactam/ampicillin	$\leq 2$	S
cefazolin	$\leq 4$	S
cefmetazole	$\leq 4$	S
imipenem	$\leq 1$	S
arbekacin	$\leq 1$	S
gentamicin	$\leq 0.5$	S
erythromycin	$\leq 0.25$	S
clindamycin	$\leq 0.25$	S
minocycline	$\leq 0.5$	S
vancomycin	1	S
teicoplanin	$\leq 0.5$	S
linezolid	2	S
levofloxacin	$\leq 0.12$	S
fosfomycin	$\leq 8$	S

MIC, minimum inhibitory concentration; S, susceptible.

(6,10). For instance, our patient presented with a normal body temperature (36.7°C) at admission, partly attributed to prior NSAID (loxoprofen) use for back pain. Nonetheless, we should always consider pyogenic spondylitis as a differential diagnosis, even in the absence of fever. Early-stage diagnostic imaging can also be inconclusive. For example, X-rays may not reveal significant changes until 3–6 weeks after symptom

onset (10). The sensitivities of CT and MRI scans are reportedly superior (65–75% and 82–100%, respectively) (11). However, their limitations often lead to delayed diagnosis, especially in emergency settings where MRI scans are not always immediately available. Our patient initially visited the emergency department 2 days before admission; despite the unremarkable findings on CT, a blood culture taken the same day returned positive, leading to the diagnosis.

Moreover, blood cultures are crucial for pyogenic spondylitis diagnosis, with reported positivity rates within 38%–78% (12,13). By identifying the causative organism, physicians can prescribe the appropriate antibiotics. Blood culture is also easier to perform than other invasive sample collection procedures, such as bone sample collection or CT-guided biopsies. Therefore, we should actively collect blood cultures when pyogenic spondylitis is suspected, even if the initial symptoms are nonspecific.

Although nonoperative treatment is effective in 90% of cases (14), surgical intervention is sometimes necessary in patients with spinal instability, neurological symptom deterioration, extensive bone destruction, epidural abscess formation, conservative treatment failure, or intractable back pain (15-17). In our patient's case, surgical drainage was considered because of the presence of an epidural abscess. However, considering the wide spread of the abscess, the orthopedic team ruled out surgical intervention as a viable option.

Treatment with ceftriaxone seemed to be effective, given the improved results of the blood test and CSF findings. However, the patient's condition deteriorated rapidly on day 12, resulting in a fatal outcome. We conducted an autopsy to determine the extent of the lesion. Numerous inflammatory cells infiltrated the brainstem (cerebellum, pons, and medulla oblongata) without bacterial presence. This inflammation seemed to cause tissue destruction and subsequent failure of critical life-sustaining functions.

Specific bacterial toxins, such as PVL and TSST-1, play a role in bone infections, particularly PVL (18). The MSSA JARB-OU3818 strain isolated in this case was positive for *egc* (*seg*, *sei*, *sem*, *sen*, and *seo*), which is typically associated with gastrointestinal symptoms, but this gene cluster was deemed less relevant to this case's pathology.

#### Conclusion

This report presents a case of pyogenic spondylitis accompanied with severe complications, including extensive epidural abscesses and bacterial meningitis, which progressed rapidly and ultimately resulted in a fatal outcome. This case underscores the importance of recognizing that pyogenic spondylitis can follow such an aggressive clinical course.

Given the rapid progression, we investigated the

pathogenic characteristics of the causative strain. Although JARB-OU3818 was negative for known cytotoxic virulence genes, such as *PVL* and *TSST-I*, it was identified as a novel ST9378. Therefore, the strain might harbor as-yet-unidentified virulence genes, highlighting the need for further research.

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## From prototype to implementation: Development of the DMIST scoring system for monitoring diabetic foot ulcers

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**Abstract:** Diabetic foot ulcers (DFUs) pose a significant health challenge, marked by high morbidity, mortality, and healthcare costs. Effective evaluation of the DFU healing process is crucial to prevent delays and enhance patient outcomes. Traditional wound healing scales like PUSH and DESIGN have proven suboptimal for DFUs, necessitating a disease-specific approach. This communication introduces a qualitative study, which served as the first step in developing the DMIST scale, a tool to monitor and assess DFUs over time. Using a morpho-qualitative analysis method, we examined 50 DFUs in 42 patients from a hospital in Tokyo, classifying ulcers by primary pathogenic factors and healing periods. Our analysis identified 8 categories and 33 sub-categories of morphological characteristics. Key findings included identification of features such as the "red ring", "hyperkeratosis", and "rolled wound edges", each affecting healing times. The DMIST scale integrates these visual signs, offering a practical tool for DFU management, particularly valuable in low-resource settings. This scale has undergone validation and refinement through international collaboration, with the aim to improve DFU patient outcomes globally. We hope the DMIST scale to be widely adapted and that our experience in its development will aid future development of wound assessment tools from various causes.

Keywords: assessment, management, wound, neuropathy, peripheral arterial disease, infection

#### Introduction

Diabetic foot ulcers (DFUs) are a major complication of diabetes, with their incidence rising substantially alongside the global diabetic population. DFUs can severely impact quality of life of those affected, limiting daily activities and potentially leading to amputation. They are associated with significant morbidity, mortality, and high healthcare costs. The protracted nature of DFUs is partly due to delayed diagnosis and inadequate care, making early diagnosis and treatment crucial. Effective evaluation of the wound healing process is essential to identify deviations from normal healing and to adjust management accordingly to avoid delayed healing.

Existing wound healing scales like the Pressure Ulcer Scale for Healing (PUSH) (1) and the DESIGN (2) for pressure ulcers, and the Southampton Wound Scoring System (3) and ASEPSIS (4) for surgical wounds, have proven valuable. However, their application to DFUs has been suboptimal. With this background, we have developed the DMIST scale, which is a disease-specific scale for monitoring and assessing the clinical course of DFUs.

The wound healing process primarily depends on the depth of the wound. Wounds that affect only the superficial dermis are healed by regeneration, while wounds that extend deeper into the dermis need to go through repair, typically involving four stages: inflammatory, proliferation, maturation, and epithelialization (healed). DFU pathogenesis involves a complex interplay between three main underlying pathogenic factors: neuropathy, angiopathy, and infection. Despite empirical knowledge of their effects on the repair process (5), the distinct impacts of these factors remain underexplored. Moreover, signs of deviation from the normal healing process by primary pathogenic factors, and their relation to healing time, are still poorly understood.

Therefore, in order to develop the DMIST scale, we first needed to identify the morphological characteristics of the healing process of DFUs by different primary pathogenic factors and at various stages of healing. This identification allowed us to select signs that are suggestive of deviation from the normal wound healing process to be included in our prototype DMIST scale. The aim of this short communication is to share this first stage of the DMIST scale development.

## Research design for developing the prototype DMIST scale

#### Morpho-qualitative analysis method

We employed a morpho-qualitative analysis method developed by our research team (6). This method uses clinical photos of lesions to create drawings, followed by providing verbal descriptions to each photo. Creating drawings helps capture small, subtle signs that may be overlooked when directly verbalizing from photos. The verbal data are subsequently analyzed using a qualitative descriptive study method.

#### Subjects and data collection process

Study subjects were recruited from patients with DFUs who visited the Dermatology Department of a tertiary hospital in Tokyo, Japan between August 2010 and January 2014. Photos of DFUs were taken during outpatient visits, with the healing period defined as number days from first confirmed visit to wound closure. DFUs were classified following the Kobe classification based on their primary pathogenic factor: Type I (peripheral neuropathy), Type II (PAD), Type III (infection), and Type IV (combination of factors) (7). Peripheral neuropathy was assessed using a Semmes-Weinstein 5.07/10 g monofilament, 128-Hz tuning fork, Achilles tendon reflexes, coefficient of variation for the R-R intervals in electrocardiogram, and nerve conduction velocity exams. Neuropathic symptoms such as pain, paresthesia, tingling, discomfort, and numbness were also recorded. PAD was assessed using ankle-brachial index (ABI), skin perfusion pressure (SPP), transcutaneous oxygen pressure  $(tcpO_2)$ , and enhanced computed tomography (CT) scan. Infection was assessed by clinical and laboratory (elevated white blood cell count and C-reactive protein) findings, and when in need, image exams (X-ray, CT, or magnetic resonance imaging) were performed.

#### Data analysis

The verbal data obtained through the morpho-qualitative analysis method were analyzed for similarities and aggregated into sub-categories and broader categories. Extracted categories and subcategories were then organized into spreadsheets based on three healing periods ( $\leq$  30 days, 31-90 days,  $\geq$  91 days) and by Kobe classification. These characteristics were examined

within and across these groups.

#### Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki, with approval by the Ethical Committee of the National Center for Global Health and Medicine, Tokyo, Japan (approval number: 727). All participants provided consent for use of their clinical data and photographs for scientific purposes.

#### Key results

#### Overview of study subjects

A total of 50 DFUs in 42 diabetic patients were recruited and evaluated. Their average age was  $65.9 \pm$ 14.1 years, with 76.1% male. The most common ulcer site was the toes (25/50, 50%), and the most common trigger was vasculopathy (9/50, 18%) followed by shoe sore (7/50, 14%).

The average follow-up time was  $77.4 \pm 90.5$  days, ranging from 1 to 377 days, with a mean interval between observations of  $24.1 \pm 38.5$  days. A total of 227 photographs were taken throughout the healing process and were included in the analysis. DFUs were classified by the Kobe classification, and there were 14 Type I, 15 Type II, 12 Type III and 9 Type IV. Twenty-two DFUs achieved complete healing, 22 were in advanced healing stages, 2 wounds progressed to gangrene, and 2 required amputation. Two participants died during the course of the study.

#### Overview of extracted morphological characteristics

Our analysis resulted in 8 categories and 33 subcategories of morphological characteristics. Table 1 presents these findings together with their definitions. Figure 1 and Supplemental Table S1 (*https://www.ghmopen.com/site/supplementaldata.html?ID=93*) present these characteristics for the three healing periods ( $\leq$  30 days, 31-90 days,  $\geq$  91 days) and for the four Kobe classification types. For the healing periods, those that reached complete healing (22 DFUs) were included in the analysis.

This study identified the different morphological characteristics of DFU healing. While some characteristics were shared, there were notable differences during the inflammatory and proliferation phases based on healing times and by primary pathogenic factors or the Kobe classification. Maturation phase characteristics were more similar across groups. Furthermore, we were able to improve the understanding of some characteristics, which have been empirically known, but have been poorly studied or documented previously, such as "red ring",

Category	Subcategory	Definitions
Depth	Dermal level	Tissue loss/damage extending to the dermis
-	Tendon level	Tissue loss/damage extending to the tendon
	Bone/joint level	Tissue loss/damage involving the bone or joint
Size	Enlargement	Increase in wound size
	Decrease	Decrease in wound size
Granulation tissue	Red granulation tissue	New connective tissue with red color, featuring proliferation of microscopic blood vessels
	Granulation tissue with swelling Bright red granulation tissue	New connective tissue with swelling due to inflammation or excessive exudate New connective tissue with bright red color, featuring excessive proliferation of microscopic blood vessels
	Granulation tissue with humpy surface	New connective tissue with a papular to podular surface in appearance
	Excessive granulation tissue: Excessive granulation tissue	Excessive growth of new connective tissue, oftentimes protruding the level of the surrounding skin
Necrotic tissue	Eschar	Thick dry/dead black necrotic tissue
	Hard slough	Hard yellow fibrinous tissue consisting of fibrin, pus, and proteinaceous material
	Soft slough	Soft yellow fibrinous tissue consisting of fibrin, pus, and proteinaceous material
	Oatmeal/porridge-like necrotic tissue	Dead tissue with oatmeal/porridge-like appearance and texture; whitish to
		yellowish in color, mushy in texture
Translucent film	Translucent film	Jelly-like translucent thin film covering the wound surface
Wound edge	Maceration	Softening and whitening of skin due to constantly wet environment
	Red ring	Wound edge that is rimmed by a thin red line /Red-rimmed wound edge
	Hyperkeratosis	Excessive keratinous proliferation on the wound edge/ layers of keratinization on the wound edge
	Rolled	Extension of the surrounding skin covering the wound edge
	Petechiae	Signs of petechiae (subcutaneous purple dots) on the wound edge
	Pink ring	New skin formation (pinkish in color) from the wound edge
	Bridging	Bridging between two points of the wound edge with new skin formation
Tunnel/ Undermining	Tunnel	Narrow passageway inside the wound resulting in dead space, occurs in one direction
	Undermining	Erosion under the wound edge, occurs in one or more directions
Surrounding skin	Pink-purple-red change in skin color	Pinkish, purplish, to reddish color change of the surrounding skin from pressure,
-	(non-infection):	ischemia, etc. but not from infection
	Pink-purple change in skin color (post-	Pinkish to purplish color change of the surrounding skin after infection; no three
	infection):	cardial signs of infection, i.e., redness, swelling, and warmth
	Redness and swelling	Reddish color change and swelling also often associated with warmth of the surrounding skin as signs of infection
	Hypernigmentation	Darkening of skin color
	Keratin flakes	Shedding of the upper keratin layer during or after inflammation
	Natural redness	Sign of inflammation due to accelerating wound healing process; natural
		redness as a result of dilation of blood vessels to allow circulating cells,
		nutrients, enzymes, antibodies, and other beneficial elements reach the wound; no signs of infection
	Hypopigmentation	Lightening of skin color
	Purpura/old bleeding	Purpura or old bleeding (still reddish in color, bleeding in the shallower level of
		the dermis compared to purpura) of the surrounding skin
	Fine lines	Lines observed in the surrounding skin during wound contraction

### Table 1. Morphological characteristics of the healing process of diabetic foot ulcers extracted from our analysis and their definitions

"hyperkeratosis", and "rolled wound edges".

#### Red ring sign

We initially hypothesized that the red ring sign is unique to wounds with underlying PAD. It was interesting however, that through our analysis, it was a shared feature across all Types of DFUs during the inflammatory phase, irrespective of the presence of PAD. Thus, this study's findings indicate that both micro-vasculopathy from peripheral neuropathy and macro-vasculopathy from PAD can lead to the presentation of the red ring sign. The red ring may be a sign that there is an imbalance in circulation, which can lead to ischemia inside the wound and delay wound healing. Abnormalities of the blood vessels in



Figure 1. Pattern diagram of morphological characteristics of the healing process of diabetic foot ulcers. (a) Based on healing duration, (b) Based on the Kobe classification.

the wound bed and wound edges of DFUs have been observed histopathologically (8).

#### Hyperkeratosis

Hyperkeratosis on the wound edges, a common feature across all groups, started from the proliferative phase until the mature phase. The mechanism of this hyperkeratosis is not well understood. There has been a report suggesting that suppression of desmocollin 1 degradation in diabetic callus may be contributing in its development (9). In a study using rat models, hyperkeratosis of wound edges was observed histologically and was considered to be one of the major causes of delayed healing (10). It is also known that excessive hyperkeratosis of wound edges needs to be treated in order to accelerate wound healing (11-13). In this study, we treated hyperkeratosis by excision, which may have resulted in shortening of healing times of some wounds. The wounds that showed slower recurrence of hyperkeratosis tended to heal quicker.

## Infection-related characteristics, including rolled wound edges

Infection-related characteristics were identified in the study. Tunnels only appeared during the inflammatory and proliferation phases of Kobe classification Types III and IV. Tunnelling is likely linked to infection, serving as a good cultivating space for bacteria (14). A rolled wound edge was found to only appear during the proliferation phase of Type III. The condition we observed is also defined as epibole in some literature, and is commonly known to be associated with infection (15). It is a condition when the upper epidermal cells roll down over the lower epidermal cells, inhibiting side-ways migration of cells (15). In a recent study by Armstrong et al., they showed a high bacterial load on wound edges and periwound (2 cm radius around the wound edge) using fluorescence-imaging (16). It may be possible that these bacteria are playing some role in altering migration of the epidermal cells. Tunnelling and rolled wound edges were linked to specific DFU types, highlighting the importance of managing infection to improve DFU healing outcomes.

#### Morphological characteristics related to healing time

Predicting healing time can aid treatment decisions. DFUs healing within 30 days were typically shallow, without severe tissue involvement or significant necrosis such as eschar and hard slough. In contrast, DFUs taking over 91 days showed deeper tissue involvement, tunneling or undermining, and unique characteristics such as petechiae during the inflammatory phase, appearance of translucent film during the proliferative phase, and a pink ring during the maturation phase. Appearance of petechiae in the periwound region can be a sign of abnormal blood vessels.

#### Limitations

In this study, the observations were made while the patients were receiving treatment accordingly to the latest standard of care, and some of these treatment methods could have affected the morphological characteristics of their ulcers. We documented treatment methods but did not reflect this in our analysis due to its complexity. Patients' follow-up intervals were not uniform, *i.e.*, it was made at the convenience of our patients, which could have led to missing some morphological characteristics.

#### Development of the prototype DMIST scale

Building on these findings, we developed the prototype DMIST scale, a disease-specific scale for monitoring and assessing clinical course of DFUs. We included

morphological characteristics such as "red ring", "hyperkeratosis", and "rolled wound edges", which were identified during the aforementioned study. These characteristics are simple to observe, and the DMIST scale is based solely on visual signs. As the global prevalence of diabetes continues to be on the rise, with projections indicating that over 90% of the increase in the diabetic population by 2045 will occur in low- and middle-income countries (*17*), our aim for the DMIST scale is to be particularly valuable for follow-up of DFU patients, especially in low-resourced settings with limited healthcare access.

#### Current status of the DMIST scale

Following this morphological study, we conducted validation studies (18), and after multiple refinements, we now have an established tool. The DMIST scale was validated and refined through international collaborations. Further studies were undertaken and it was used to test the relationship between items of DMIST and healing of DFUs after 4 weeks (19) and the quality of life of patients living with DFUs (20). We have presented the tool at several conferences, and it is now beginning to be adopted by footcare clinics across Japan and other countries.

In conclusion, the steps to develop a disease assessment tool require verification of reliability and validity. While research has explored the pathophysiology of DFU chronicity, a substantial gap remains in translating this knowledge into real-world clinical practice. This study provides valuable insights into the morphological characteristics of DFU healing, identifying indicators that supported development of the DMIST scale for better DFU management. The prototype DMIST has since undergone rigorous validation of its reliability and validity in its current form. Our hope for the DMIST scale is that it will be widely adopted to improve patient outcomes and well-being for those with DFUs. Additionally, we believe our experience in its development will aid future development of wound assessment tools for various etiologies.

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### A path analysis of factors influencing life satisfaction among patients with narcolepsy in Japan

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**Abstract:** Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness, impaired psychosomatic functioning, and a reduced quality of life. We identified several factors influencing life satisfaction and suggested ways to improve it in patients with narcolepsy. To the best of our knowledge, this is the first study to measure life satisfaction using path analysis. A questionnaire was administered to 87 individuals diagnosed with narcolepsy. A hypothetical model was tested to determine its effect on life satisfaction. The results of the path analysis were  $\chi^2 = 11.94$  (p = 0.53), GFI = 0.96, AGFI = 0.92, CFI = 1.00, and RMSEA = 0.00. The overall effects were impact on activities ( $\beta = 0.41$ ), self-acceptance ( $\beta = 0.36$ ), adaptive attitude ( $\beta = 0.36$ ), excessive daytime sleepiness ( $\beta = 0.13$ ), mental disorder ( $\beta = 0.10$ ) and attention-deficit/hyperactivity disorder ( $\beta = 0.08$ ). The results indicate that medical conditions such as sleepiness do not impair life satisfaction. This study suggests that life satisfaction can be increased through self-understanding and engaging in adaptive cognition.

Keywords: narcolepsy, life satisfaction, adaptation, self-perception, mental-health

#### Introduction

Narcolepsy is an autoimmune disease that targets hypocretin/orexin-producing neurons within the hypothalamus (I). It is characterized by difficulty staying awake during the day. Some individuals with narcolepsy experience a sudden loss of muscle tone triggered by strong emotions, referred to as cataplexy (2). The worldwide prevalence is approximately 1 in 2,000, while in Japan, it is approximately 1 in 600 (3). The average age of onset in Japan is 17.8 years (SD 8.8) (4).

The most significant impact of narcolepsy is role limitations (5), affecting activities such as performing housework, attending school, and working. Depression and anxiety tendencies are higher in patients than in the general population (6). Recently, it has been reported that the hyperactivity/impulsivity and inattention symptoms observed in individuals with attention-deficit/ hyperactivity disorder (ADHD) are genetically related to narcolepsy (7,8). People with ADHD experience a decline in executive function and impairment of social functions such as academics and employment. Studies have reported that the quality of life (QOL) of patients with narcolepsy is low. In addition to sleepiness, cooccurring disorders such as depression, other mental disorders, and ADHD may lead to a reduced QOL.

QOL is a comprehensive assessment of diverse aspects of life, including health, economic conditions, the environment, education, social relationships, and psychological state. It includes objective living conditions (e.g., quality of housing, income, and education level) and subjective assessments (e.g., wellbeing and stress levels). In contrast, life satisfaction is a subjective assessment of an individual's life satisfaction. It considers the totality of past experiences, current circumstances, and prospects, heavily depending on the individual's feelings and values. Even if QOL is low, life satisfaction may remain high depending on individual values and adaptability. Even with treatment, the QOL of patients with narcolepsy does not recover to general population levels (9), and it is challenging to improve comorbid disorders such as ADHD. We decided to focus on life satisfaction from the perspective of patients, which leads to well-being.

Research explicitly focusing on life satisfaction in patients with narcolepsy is limited. A PubMed<sup>®</sup> search until 2018 revealed only one review article with either life satisfaction or well-being in the title. That study

(10) suggested that children with narcolepsy are at a significant risk of cognitive impairment and emotional problems such as depression, anxiety, and low selfesteem. Currently, no studies have examined approaches to improve life satisfaction in patients with narcolepsy.

It is assumed that the life satisfaction of patients with narcolepsy is related to their medical conditions, comorbid disorders, and cognitive and health problemrelated daily activities. Clarifying these associations will contribute to improving life satisfaction. Therefore, this study aimed to identify factors that influence life satisfaction in patients with narcolepsy.

#### Assessment

Participants were asked to provide basic demographic information and medical history (narcolepsy symptoms, disease duration, frequency of cataplexy, and presence of ADHD or mental disorders). Narcolepsy, mental disorders, and ADHD were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which are based on a questionnaire survey and a history of upbringing conducted by a health care provider. However, this point was self-reported.

Excessive daytime sleepiness (EDS) was assessed using the Japanese Epworth Sleepiness Scale (JESS), a self-reported questionnaire. This subjective measure of daytime sleepiness was developed by Johns in 1991 (11). The JESS uses eight questions to assess the likelihood of falling asleep and encompassing daily situations. Respondents were asked to rate the items on a 4-point scale (0-3). A JESS score of 16 or higher was defined as EDS in this study, as a JESS score of 16 or higher is strong enough sleepiness to cause a traffic accident while driving (12). Impact of the activities, such as how their health problems affected productivity in regular unpaid activities or school life using a 0 to 10 Visual Analogue Scale (VAS). We asked subjects to respond to the statement of self-acceptance using a 5-point Likert scale, ranging from 1 = strongly disagree to 5 = strongly agree. Adaptive attitude was measured using a scale developed by Suganuma et al. (13). This scale measures adaptive attitudes, a positive attitude that accepts the negative aspects of the self and the situation as they are but does not dwell on them. Higher scores indicate a more accepting attitude toward the self and the situation while resigning oneself to it.

We used the Life Satisfaction Scale (SWLS) to measure how the subjects evaluated their lives. The SWLS, developed by Diener *et al.* in 1985, is selfadministrated and is a short, 5-item instrument that uses 7-point Likert scale responses (*14*). The higher the score, the greater one's satisfaction with life. The Japanese version of SWLS was used in this study.

This study was approved by the ethics committee of Saitama Prefectural University (No. 19122) and administered by the Japanese Ministry of Health, Labor, and Welfare Ethical Guidelines for Medical and Health Research involving Human Subjects.

The data was analyzed with descriptive statistics. Path analysis was used to explore the variables' interrelations and verify the associations between the variables and the SWLS score. Path analysis used variables significantly different in the Mann-Whitney U test, correlation analysis, and EDS, as they are symptoms specific to narcolepsy. Standardized regression weights were used to represent the path coefficients between variables with p < 0.05.

#### Overview of the subjects

The study included 87 patients (62.1% female). The mean age of the patients was 35.0 (SD 10.0) years, and 64 patients (73.6%) had narcolepsy with affective cataplexy. Among the participants, 89.7% were currently undergoing evaluation treatment. Participants with EDS were 50 (57.5%), and 12 (13.8%) of the cases had a mental disorder, while eight (9.2%) had ADHD. Disease duration was less than five years in 1.1%, more than five years in 80.5%, and 5 to 10 years in 18.4% of participants.

#### Level of life satisfaction

The average SWLS score was 19.1 (SD 7.8) for men and 17.5 (SD 6.9) for women. This value was significantly lower than that for workers over 20 years of age doing desk work in Japan (mean 21.1, p < 0.01) (15).

## What is related, and how does it affect life satisfaction?

Mental disorders, ADHD, and their impact on activities, self-acceptance, and adaptive attitudes were associated with life satisfaction. However, the impact on daily activities, self-acceptance, and adaptive attitudes had independent effects on life satisfaction.

The Mann-Whitney U test showed a significant difference between mental disorders (p = 0.04) and ADHD (p = 0.02). There were no significant associations between SWLS and sex (p = 0.45), cataplexy at least once per week (p = 0.68), disease duration (p = 0.68), or EDS (p = 0.08). Spearman's Correlation analysis showed that impact on activities ( $\gamma = 0.43$ ; p < 0.01), self-acceptance ( $\gamma = 0.53$ ; p < 0.01), and adaptive attitude ( $\gamma = 0.49$ ; p < 0.01) were significant correlations. Age was not significantly correlated with SWLS ( $\gamma = 0.04$ ; p = 0.71).

In this hypothetical model,  $\chi^2 = 11.94$  (p = 0.53), GFI = 0.96, AGFI = 0.92, CFI = 1.00, and RMSEA = 0.00; thus, the model met all the criteria for this adoption (Figure 1). The estimated magnitudes of the standardized direct, indirect, and total effects were based on the path coefficients in Table 1. The direct effects were adaptive attitude ( $\beta = 0.36$ , p < 0.01), impact on activities ( $\beta =$ 



Figure 1. Path model of life satisfaction in patients with narcolepsy. The effects on the life satisfaction of patients with narcolepsy were analyzed: EDS increased the impact on activities, ADHD decreased self-acceptance, and mental disorders decreased adaptive attitudes. The impact on activities reduced life satisfaction, whereas self-acceptance and adaptive attitude contributed to increased life satisfaction.

0.28, p < 0.01), and self-acceptance ( $\beta = 0.28$ , p = 0.04). In contrast, indirect effects had an impact on activities ( $\beta = 0.13$ ), self-acceptance ( $\beta = 0.16$ ), mental disorder ( $\beta = 0.10$ ), and ADHD ( $\beta = 0.08$ ). The overall effects were impact on activities ( $\beta = 0.41$ ), self-acceptance ( $\beta = 0.36$ ), adaptive attitude ( $\beta = 0.36$ ), EDS ( $\beta = 0.13$ ), mental disorders ( $\beta = 0.10$ ), and ADHD ( $\beta = 0.08$ ).

#### How can life satisfaction be increased?

Reducing the impact of health problems on daily activities and enhancing adaptive cognition are essential for improving life satisfaction. Some patients with chronic diseases rate their condition as healthy (16), and individuals with disabilities have reported a high quality of life after coming to terms with their disability (17). Considering this, it is expected that addressing the limitations in daily activities, occasionally accepting them, and fostering psychological receptiveness can lead to improved life satisfaction.

A challenge of this study is that it failed to identify measures to reduce impact of daily activity-related factors on life satisfaction. Dodel *et al.* noted that sleepiness was not significantly associated with health function or quality of life as measured by the 36-item Short Form Health Survey (SF-36) (18). Similarly, this study found that the effect of sleepiness on life satisfaction was limited ( $\beta = 0.13$ ). While the sleepiness inherent in narcolepsy can affect daily life, it may not be a major issue in a broader context. Therefore, it is necessary to focus on factors other than sleepiness. However, this study did not examine effects on activities beyond sleepiness and cataplexy. Future research should also consider other factors that may influence patient activity.

In conclusion, we conducted a path analysis to examine factors associated with life satisfaction in

 Table 1. Summary of the direct, indirect, and total effects on life satisfaction

		Effects	
Variables	Direct	Indirect	Total
Mental disorder		-0.10	-0.10
ADHD		-0.08	-0.08
EDS		-0.13	-0.13
Impact of activities	-0.28	-0.13	-0.41
Self-acceptance	0.20	0.16	0.36
Adaptive attitude	0.36		0.36

The direct, indirect, and total effects of each variable on life satisfaction in the path analysis are described. The strongest overall effect on life satisfaction was the impact on activities at -0.41, with self-acceptance and adaptive attitudes at similar levels at 0.36.

Japanese patients with narcolepsy. Our study gives hope that patients can achieve high life satisfaction, regardless of their medical condition. Excessive daytime sleepiness affects daily life activities, although its effect on life satisfaction is low. Adaptive attitude and self-acceptance played essential roles in life satisfaction. Reducing the impact on activities is critical to improving life satisfaction; however, what content influences activities at this stage is unclear. They are expected to achieve high levels of life satisfaction by accepting themselves and changes in their lives regardless of sleepiness. In the future, it is necessary to propose specific approaches to increase the flexibility of patients with narcolepsy and to identify factors that influence their daily life activities.

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# Comprehensive multidisciplinary approach in the long-term hospitalization of a child with obsessive — compulsive disorder and autism spectrum disorder: Emphasizing nursing practice

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**Abstract:** This article presents the case of a boy diagnosed with both obsessive–compulsive disorder (OCD) and autism spectrum disorder. Long-term hospitalization was required to improve the patient's OCD symptoms and family relationship. In his last year of compulsory schooling, a multidisciplinary team, led by a nurse, took various approaches to help him self-determine his pathway. In their role of assisting the patient with daily living, the nurses were at risk of becoming involved in his compulsive behavior and developing negative feelings. To support his self-determination, having a mutually supportive environment was essential between the multidisciplinary team and team members, which included discussing his daily living concerns and venting out negative feelings. In this case, ongoing dialog with the medical staff was important for the individual and parents to move forward positively within a supportive framework.

Keywords: child and adolescent psychiatric nursing, self-determination, multidisciplinary team

#### Introduction

This article presents the case of a boy diagnosed with both obsessive-compulsive disorder (OCD) and autism spectrum disorder (ASD) without intellectual disabilities. We aimed to derive effective nursing interventions for the patient by reviewing the nursing process, symptoms, and treatment from admission to discharge in the Child and Adolescent Psychiatric Ward.

During the patient's third hospitalization, we focused on employing a multidisciplinary approach and nursing interventions related to self-determination and parent-child relationships, including his post-discharge life (Table 1). Furthermore, to ensure the confidentiality of individuals, some information was anonymized while retaining the content's integrity.

#### **Clinical setting**

The Child and Adolescent Psychiatric Ward at Kohnodai Hospital, National Center for Global Health and Medicine, featured 45 beds with an in-hospital school. The primary nursing system assigns one nurse to oversee each patient from admission until discharge. The unit comprises 11 four-bed rooms and seven private rooms and accommodates patients up to the third grade of junior high school.

#### **Clinical case**

#### Developmental and concurrent medical history

A 15-year-old boy was admitted to our unit because of severe OCD symptoms. The patient's medical history revealed signs of obsession with food and hypersensitivity to sound during infancy. Furthermore, the patient exhibited unusual behaviors, such as disrobing while urinating and changing clothes. In year X-7, the patient experienced bullying at school, leading to difficulties in eating. At home, the patient resorted to aggressive behaviors toward his family and spent nearly half a day in the bathroom because of anxiety. The patient was admitted three times due to deteriorating symptoms and family relationship disruptions.

Previous hospitalization

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#### Table 1. Multidisciplinary approach led by nurses during the patient's third hospitalization

Time	May, Year X	May to July, Year X
His condition	<ul> <li>Overadaptation to hospitalization</li> <li>Intense anger toward his parents for forcing him to be hospitalized</li> </ul>	<ul> <li>End of overadaptation and relapse of compulsive behavior</li> <li>Fear of excessive seclusion and need of assurance that he will not be secluded</li> </ul>
Details of intervention	<ul> <li>Eased the tension of his parents and recommended rest</li> <li>Communicated information about his hospitalization to the family under visitation restrictions</li> <li>Assessed his readiness to meet with family members and informed him about their visits</li> <li>Addressed the mother's concerns and challenges in interacting with her son</li> </ul>	<ul> <li>Staff shared frustrations with him openly, rephrasing them into simple and polite language</li> <li>Informed the patient that he was beyond the fear of isolation stage and encouraged him to focus on life after graduation</li> </ul>
Time	August to October, Year X	November, Year X to March, Year X+1
His condition	<ul> <li>Began to talk about his worries and career path</li> <li>Recognized and included by other hospitalized children</li> <li>Reconciliation with parents</li> </ul>	<ul> <li>Accepted the family's policy of not living together</li> <li>Emergence of anxiety and frustration after discharge from the hospital</li> <li>Increased burden on him and his parents due to unfamiliar high school entrance examinations and group home search</li> </ul>
Details of intervention	<ul> <li>Listened to him and worked with him on how to respond about friendship problems</li> <li>Encouraged him to plan and implement specific actions for his high school application independently</li> <li>Helped him organize what he intended to communicate with his parents during their initial reconciliation</li> <li>Established and supported a minimum in-hospital school attendance time collaborated with his HRT</li> </ul>	<ul> <li>Collaborated with local medical and social services to initiate the search for a group home after discharge</li> <li>Shared information with in-hospital classes to prepare him for the high school transition led by his family</li> <li>Assisted him in developing strategies to maintain the schedule he established</li> <li>Engaged in phone conversations with him and his parents to methodically discuss and prioritize specific actions</li> </ul>

The patient's first hospitalization occurred during elementary school (year X-5 to year X-3). Before admission, the patient experienced a life-threatening decline in food intake. Upon admission, behavioral restrictions and nutritional management were imposed. As the patient recovered, he attended an elementary school in the hospital. After his initial hospital discharge, the patient gradually became unable to attend school and exhibited destructive behaviors again in the house. Consequently, the patient was re-hospitalized (year X-3 to year X-1). Hospital staff encouraged the patient to become more independent in his daily routines, including commuting to school and attending structured interview sessions. Family support efforts aimed at easing the mother's burden, promoting family reunification, and introducing home nursing care upon discharge were administered.

After the previous discharge, the patient's life deteriorated rapidly. The patient became fixated on mirrors and could no longer attend in-hospital classes. Family accommodation became severe, and the patient's parents were exhausted. The patient repeatedly sought assurances from his parents that he would not be hospitalized again and insisted on providing promises. The home nursing service introduced upon discharge from the hospital was discontinued after 2 months. The patient and his parents also refused home visits by the homeroom teacher (HRT).

#### *Third Hospitalization: Year X to X+1 May, Year X*

The patient was hospitalized for the third time during ninth grade. Upon hospitalization, the patient exhibited remarkable adaptability, attending in-hospital school daily and participating in various activities. Despite not bathing for several months at home, the patient began to bathe once a week following admission. However, the patient remained isolated from other children in our ward and school. The patient harbored resentment toward his parents, often repeating, "My parents promised not to hospitalize me, but they did". The patient refused visits from his parents, and his mother also hesitated and dreaded seeing him. The patient's father was the sole visitor responsible for exchanging daily items with the nurses. Simultaneously, the parents maintained regular meetings with the attending physician. The multidisciplinary team, led by nurses, provided information about his daily life in the hospital to his parents. In particular, the nurses approached the parents in an atmosphere of informality and small talk. They attended to the mother's psychological anxieties when dealing with her son and encouraged her to rest. Furthermore, they assessed the patient's readiness to meet with family members and informed him about their visits.

May to July, Year X

After 2 months of hospitalization, the patient experienced challenges with daily activities. Over time, the patient struggled with timed activities, such as bathing and attending school; when the patient could not perform well, he placed the blame on medical staffs. The patient developed an intense fear of seclusion and attempted to elicit the word that he would not be isolated by hounding the medical personnel. The patient found it challenging to cope with the various limitations of infection control prevention measures during his hospitalization. The patient's unmet wishes fueled frustration and anger. Furthermore, his autistic tendencies not only prevented him from understanding what the other person was warning him about but also risked contributing to panic by focusing only on the angry expression on the other person's face: This had been observed many times in previous interactions with his mother. Some staff nurses were unpleasant because of his way of treating them as if nothing had happened the day after an intense outburst. The multidisciplinary team, led by nurses, shared staff frustrations about the patient openly. The primary nurse, who carefully watched her tone and facial expressions, then rephrased their frustrations into simple and polite language to the patient. The medical staff also informed the patient that he was beyond the fear of isolation and encouraged him to focus on life after graduation. Furthermore, the primary nurse and HRT had frequent contact and exchanged information about hospitalization and school life.

#### August to October, Year X

The patient began to talk about his age-related friendship problems as he made friends in the hospital. The medical staff listened to the patient and worked with him on how to respond. The patient gradually began to discuss his career path concerns and expressed a desire to attend high school. However, the patient still refused to see his family. The patient's psychiatric social worker (PSW) continued to work with him to reunite him with his parents in preparation for his discharge and career path. The patient organized his interactions with the PSW by talking to his nurse. During this period, the patient often used the term "first reconciliation with his parents". The patient always felt that his parents were deprived of making decisions for him. Therefore, the patient decided to reconcile with his parents for now as a means of gaining access to higher education, although the patient still felt resentful toward them.

The multidisciplinary team helped him organize what the patient intended to communicate to his parents. Furthermore, they encouraged him to plan and implement specific actions for his high school application independently. Furthermore, they collaborated with the patient's HRT and supported minimum in-hospital school attendance to encourage consistent school attendance. After the initial reconciliation, the patient resumed communication with his parents as if nothing had happened. He had a haircut and shave, which he had not done for years, in preparation for the examination.

#### November, Year X to March, Year X+1

The parents complained to the doctor that they could not live with their son. The patient expressed, "at this point, I don't think he would do well back home". The patient admitted that he was not sure. As a result, it was decided to look for a group home as a place for the patient to live after discharge from the hospital. Throughout the patient's examination preparation and housing search, he experienced multiple challenges with deadlines, which triggered frequent outbursts; however, the patient never stopped attending his inhospital classes.

The multidisciplinary team, led by nurses, provided information about the patient's concerns or considerable points regarding communal living, and the patient continued to work with staff from the local mental and welfare services through his PSW. Furthermore, they assisted him in developing strategies to maintain the discharge schedule he established. In particular, the PSW followed the patient on his frequent outings to taking his examinations and finding a group home, gradually delegating this role to his parents. The patient's HRT also continued to meet with his parents. Nurses confirmed the appropriate use of abortive medication when going out or staying overnight. Furthermore, they engaged in calmed conversations to prevent arguments between the patient and his parents from developing to methodically discuss and prioritize specific actions.

The patient successfully gained acceptance into high school and celebrated with friends at the ward's farewell party. However, due to his age and medical condition, the patient could not find a suitable group home during his hospitalization. Consequently, the patient was discharged home temporarily, which his parents accepted. His mother, who had been stubborn toward him, was pleased with the progress that the patient had made during this hospitalization. The patient remained at home without causing inconvenience to his family while awaiting placement in a group home.

#### Medication

Pharmacotherapy included paroxetine (50 mg), levomepromazine (50 mg), and haloperidol (9 mg).

#### Discussion

Early intervention for OCD in children is important not only to reduce the duration of untreated psychosis but also to prevent the loss of important opportunities for growth and development, including school life (1,2). This case was accessed at an early stage in a child psychiatry outpatient clinic, and treatment was initiated; however, the long-term intervention by a multidisciplinary team continued until the end of the patient's compulsory schooling year. The prolonged duration of child psychiatric hospital stays influenced the severity of the patient's psychiatric issues and family functioning challenges, such as limited community resources and low child-rearing capacity (3). However, note that during extended hospitalizations, children often experience improvements in life functioning through group activities and school life (3).

This hospitalization was also crucial for him to explore self-determination and his chosen way of life. The medical staff pulled the patient out of a stalemated family relationship and provided him with an environment conducive for integration with his peers, which he had been prevented from doing due to the intensity of his severe symptoms. The patient's experience of recognition from other children provided him with a sense of belonging and self-affirmation. In particular, the nurses provided unwavering support to rebuild his disordered lifestyle and self-esteem while focusing on developmental milestones.

Nurses in child psychiatry play a vital role in offering support while striking a balance between adhering to the therapeutic structure of the ward and nurturing the child's autonomy (4). However, because of the nurses' role in assisting with daily living, they were at risk of becoming involved in the patient's intense compulsive behavior and developing negative feelings. Child psychiatric nurses have been reported to be more exposed to occupational stress and are at higher risk of burnout (5-7). Therefore, a multidisciplinary team and an environment conducive for mutual support among team members, including sharing of concerns and venting out of negative emotions, were essential for the nurses to remain calm and provide the patient with consistent care.

In Japan, parents are usually expected to continue caring for their children after compulsory education ends. However, family involvement in children with OCD or ASD disrupts and exhausts the family's daily life (8-11). The patient's parents expressed difficulties in living with their son again. Therefore, medical personnel had to find not only a place for the patient to go to school but also a group home; however, finding a residential facility that accepts young individuals with mental illness or disabilities is challenging (12). Although the medical staff encouraged the family to take a break, they continued to support the family initiative during this important phase of the patient's career decision-making. The nurses assessed the parents' readiness to engage with their child and empathized on the burden of supporting their child's life.

The roles of child psychiatric nurses were to share information about hospital and school life with other staff members and the patient's parents to maintain daily activities after discharge. The ongoing dialog with the medical staff was important for the patient and his parents to move forward positively within a supportive framework.

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## The Academic Research Organization Alliance for Southeast and East Asia (ARISE) in the new era: An international trials network towards pandemic preparedness

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**Abstract:** The Academic Research Organizations (ARO) Alliance for Southeast and East Asia (ARISE), established in 2021, is a network of academic research organizations in Southeast and East Asia. Its founding vision was focused on conducting effective, high-quality clinical research and providing timely access to new medicinal products during health crises. Through its focused efforts, ARISE has fostered regional cooperation and contributed to implementing clinical trials of medical products in its network. In response to global health challenges, the Government of Japan is establishing a new organization, the Japan Institute for Health Security, with functions encompassing infectious disease control and pandemic preparedness. As ARISE continues to fulfill its mission of addressing emerging infectious diseases, the ongoing changes in its founding organization will significantly impact its operations. With this article, we aim to highlight ARISE's achievements in its first two years and to explain how its strategy has been adapted to the new organizational structure and evolving global health landscape. ARISE strives to strengthen its network collaboration and further enhance the ability of member organizations to respond rapidly and effectively to future health emergencies.

Keywords: pandemic preparedness, infectious diseases, clinical trials, ARO, ARISE

#### Introduction

The Academic Research Organizations (AROs) Alliance for Southeast and East Asia (ARISE) is a network of AROs in Southeast and East Asian countries. It is an initiative of the Japanese National Center for Global Health and Medicine (NCGM), founded upon the Asia Health and Wellbeing Initiative in 2021. ARISE's founding vision and mission were primarily focused on the performance of effective, high-quality clinical research and the provision of timely access to new medicines for Asian patients during health crises (*1-3*). To fulfill ARISE's function and operations in pursuit of its original mission, the Department of International Trials under the Center for Clinical Sciences at the NCGM serves as ARISE's secretariat (*1,4*).

ARISE's core mission aligns with a global imperative, the "100 Days Mission", launched to enable the development and deployment of new diagnostics, therapeutics, and vaccines within 100 days of a pandemic. This shared goal underscores the importance of timely access to new medical products during emerging health crises. The lessons learned from the COVID-19 pandemic have led Asian countries to recognize the major challenges in managing such outbreaks and the important role of vaccine development during a pandemic. To fulfill the 100 Days Mission, Southeast Asian countries have identified that strengthening regional collaboration ties and clinical research networks will facilitate knowledge sharing and research collaboration (1,5). ARISE's role is pivotal in this context and can contribute significantly to identifying and mitigating emerging diseases in the region.

As ARISE continues to fulfill its mission to address emerging diseases, ongoing changes in the structure of its founding organization, the NCGM, will substantially impact its operations. These changes reflect the Japanese Government's efforts to prepare for future pandemics and to foster collaborations with other countries in the region. In 2022, Prime Minister Fumio Kishida took a significant step toward bolstering Japan's preparedness for future infectious disease crises by establishing a specialized, world-class science center (6). In response to the Prime Minister's Declaration, in 2023, the Minister of Health, Labour, and Welfare launched "T-Vision", which is the strategic framework of the new organization centered on health security (7). Under this initiative, a new organization, the Japan Institute for Health Security (JIHS), will be formed in April 2025 by merging two national centers specializing in infectious disease treatment and research: the NCGM and the National Institute of Infectious Diseases. The founding of the JIHS will be a notable milestone in Japan's response to public health emergencies. It will perform three critical functions: i) strengthening the collection and evaluation of data on infections in Japan and overseas; *ii*) establishing a platform for the promotion of research and development; and *iii*) forming the core of the clinical trial network in the region (7). This article aims to highlight ARISE's achievements from 2021 to 2023 and explain how ARISE is adapting its strategy within the new organizational framework.

## ARISE achievements – The first two years of its journey

In its first two years, from 2021 to 2023, ARISE actively implemented its strategies, achieved key milestones, and reinforced its network. Through focused efforts, it has promoted regional cooperation, contributed to implementing clinical trials for medicines and medical devices, and fostered a collaborative and supportive environment for clinical research. These achievements demonstrate ARISE's effectiveness in advancing its mission and contributing to the strengthening of regional collaboration in the field of clinical research.

# Establishment and fostering of a regional network of AROs

Since its establishment in 2021, with the participation of 10 institutions, ARISE has grown to 14 member organizations (Figure 1) and established collaborative offices in four countries to further enhance its regional presence and deepen its engagement with member organizations. ARISE also continued to strengthen cooperation with international organizations and networks, such as the Clinical Research Initiative for Global Health, and the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital, and Harvard, and to engage with important organizations in Japan. This growth reflects its impact and potential of meeting the current demand in the healthcare landscape in Asia, as well as its contribution to the global movement towards more effective clinical research.

#### Promoting clinical research activities in the region

ARISE has affirmed its important role as an academic research-support platform, an initiative that is paving a way for improving access to medicines and medical



Figure 1. ARISE network map and member organizations in 2024. Japan: ① National Center for Global Health and Medicine. ② Nagasaki University. ③ Kyushu University. ④ International University of Health and Welfare. ⑤ Osaka University; Indonesia: ⑥ Faculty of Medicine, University of Indonesia, ⑦ Mochtar Riady Institute for Nanotechnology; Malaysia: ⑧ Clinical Research Malaysia. ⑨ University of Malaya Medical Center; Thailand: ⑩ Faculty of Medicine, Siriraj Hospital, Mahidol University; The Philippines: ⑪ Corazon Locsin Montelibano Memorial Regional Hospital. ⑫ University of the Philippines Manila. ⑬ West Visayas State University; Vietnam: ⑭ Bach Mai Hospital.

devices in the region. Through strong collaborations with member organizations from Indonesia, Japan, Malaysia, the Philippines, Thailand, and Vietnam. ARISE has facilitated various forms of clinical research activities with a strong focus on addressing infectious diseases ( $\vartheta$ ). Even during the COVID-19 pandemic, ARISE demonstrated its ability to facilitate research collaboration between its members in the network and Japanese pharmaceutical companies, which contributed to the development of medicine and medical devices, essential components of medical countermeasures to outbreaks ( $\vartheta$ -12).

#### Enhancing clinical research capacity

At its inception, ARISE served as a central network to connect and enhance collaboration between its members and other organizations while emphasizing capacity building within the network. Several training sessions for clinical research professionals were implemented based on international standards, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), and local regulatory requirements. The training consisted of a mixed model, the "Evolving Partnership Training", which reached more than 2,000 clinical research professionals in the region (11). Moreover, ARISE member organizations joined the global project to translate the Joint Task Force Core Competency framework into the various languages of these clinical trial professionals, making it accessible to a larger number of professionals (13).

ARISE facilitates communication between its members and regional health regulatory authorities by providing a space in which they can interact directly. A joint symposium with the Japanese Pharmaceuticals and Medical Devices Agency, a regulatory authority for pharmaceuticals and medical devices, provided member organizations with the knowledge needed to address the regulatory challenges of conducting clinical trials in the region. The symposium also highlighted the importance of regulatory harmonization and adherence to Good Clinical Practice Guidelines to promote high-quality clinical research and ensure early access to medicines for Asian populations (*9,10*).

# ARISE in the evolving era: A rising alliance for pandemic preparedness

Previous outbreaks, such as the SARS and Ebola outbreaks and the recent COVID-19 pandemic, showcased the severity of economic, social, and healthcare burdens posed by emerging infectious diseases (14). Moreover, globalization exacerbates the spread of diseases, rendering preparedness for future pandemics more increasingly crucial, especially as the timing and severity of the next pandemic remain unknown. To effectively address these challenges, ARISE has recognized its crucial role under the new organization, the JIHS, and its responsibility to make the collaboration among its members more cohesive. Therefore, ARISE will continue fulfilling its mission while upgrading its various functions to contribute significantly to pandemic preparedness in the region.

With the strong collaboration among its member organizations in Asia, ARISE provides a platform to promote research and development in the region, with a primary focus on the development of therapeutics, medicines, and vaccines for infectious diseases. ARISE fosters an environment that encourages innovative research and collaboration to address the health challenges in the field of infectious diseases. Moreover, as the core role player in clinical research on infectious diseases in the region, ARISE will continue to play an important role in coordinating and enhancing its network to improve the efficiency and effectiveness of clinical research.

The ARISE strategic plan for 2024-2025 prioritizes the abovementioned JIHS functions and focuses on the following: *i*) strengthening the clinical trial network in the field of infectious diseases, particularly with partners in Asian countries; *ii*) promoting cooperation in clinical trials; *iii*) enhancing emergency response capabilities; *iv*) improving operational efficiency for clinical trials; and *v*) enhancing capacity building for human resources among member organizations. To achieve these goals, ARISE aims to facilitate joint research projects on emerging infectious diseases, vaccine development, and therapeutic interventions. Additionally, it will organize symposiums and seminars and provide technical support for researchers and healthcare professionals to enhance their skills and expertise in clinical research. Furthermore, ARISE will be committed to strengthening its partnerships with governments, academic institutions, and industry stakeholders to ensure that its efforts align with the broader goals of the regional and global health agendas.

Targeting both the opportunities and challenges posed by the new structure of its founding organization is necessary in order to fulfill these expectations. As they share the same vision and mission, ARISE will seek more support from its founding organization, in the form of invaluable guidance, infrastructure, or financial assistance. Additionally, being part of a larger organization may enhance ARISE's visibility and influence, leading to greater recognition and support for its activities. Thus, ARISE will look to strengthen its network and expand its collaboration with other organizations to make a bigger impact.

Despite its opportunities, ARISE has identified potential obstacles to achieving its mission. Differences have been observed among the member organizations in terms of the regulatory approval process and clinical research capabilities. These barriers can lead to difficulties in involving all members in a unified platform. To overcome these challenges, ARISE aims to develop workable approaches and create relevant strategies to adapt to the wide range of capabilities and specific needs of each member.

By implementing a multifaceted strategy, ARISE aims to develop an epidemic-ready platform for clinical trial operations with AROs and to promote clinical trials for the development of diagnostics, treatments, and vaccines for infectious diseases in Asia. These efforts will enhance its ability to immediately respond to future pandemics within the region and mitigate the threat of emerging infectious diseases.

#### Conclusion

ARISE has demonstrated its pivotal role in advancing clinical research and promoting the development of medicines and medical devices in Asia. Committed to adapting its strategies to align with the emerging priorities of the soon-to-be-established JIHS, ARISE recognizes its position as an impactful network for pandemic preparedness. Through continued innovation and collaboration, ARISE strives for a future in Asia in which everyone is protected from health emergencies and has equal access to vaccines, new medicines, and treatment methods.

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# Seven-year experience in pathology capacity development project including education for pathology residents and pathology technologists in Cambodia: Challenges and opportunities

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**Abstract:** This article discusses a 7-year (2017–2023) collaborative project aimed at pathology capacity development in Cambodia, where the pathology workforce is limited due to historical and infrastructural challenges. Cambodia's increasing cancer burden necessitates the expansion of pathology services; however, the country has only a small number of health professionals related to pathological services. Since 2017, the project, funded by Japan's Ministry of Health, Labor, and Welfare, has involved Japanese pathologists providing lectures and technical advice and Cambodian pathologists gaining training in Japan. Over time, the project expanded to support both pathologists and pathology technologists, focusing on capacity building, through a residency program for pathologists and a bridging course for laboratory technologists. The project faced several challenges, including maintaining the quality and sustainability of education, improving practical training environments, and addressing the international migration of a trained workforce. Despite these obstacles, the program trained several residents and led to the development of educational materials. The project also highlighted opportunities to mobilize Cambodian pathologists working abroad and incorporate digital technology into the education system. The article concludes that strengthening the local pathology workforce requires systemic changes, including developing the capacity of Cambodian pathologists abroad as a resource for education and service delivery.

Keywords: Cambodia, pathology workforce, continuing education

#### Introduction

Improved pathological capacity is critical to correspond to the increased demand for cancer diagnosis and conditions that require a pathological diagnosis; however, many low- and middle-income countries have limited resources to strengthen their pathology services (1). In Cambodia, with the epidemiologic and demographic transitions, the burden of cancer is increasing, and there is a growing demand for scaling up cancer management (2), resulting in the urgent need to strengthen pathology services in the country. Unfortunately, pathology is one of the neglected fields in the country. Combined with the history of the Khmer Rouge, which left the country with few pathologists, the number of pathologists in Cambodia is tremendously limited (3).

In 2014, there were only four Cambodian pathologists providing pathology services (3). In 2017, the National Center for Global Health and Medicine (NCGM) in Japan started a collaborative project with the University of Health Science (UHS), a national university in Cambodia, to support pathology education for residents and pathology technologists (NCGM was reborn by merging with the National Institute of Infectious Diseases and became the Japan Institute for Health Security (JIHS) in April 2025). This article describes our 7-year experience of pathology capacity development, including residents' and technologists' education in partnership with a national university and the NCGM. We also describe some challenges and opportunities identified through the project implementation process.

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#### Pathology education in Cambodia

Only one pathology residency program, provided by the UHS, is available in Cambodia. For the first batch of a residency program at the UHS, with a 4-year curriculum, residents were selected in 2014; the program started in 2015. Although the well-structured curriculum developed by a foreign consultant was available, the UHS initially assigned only one pathologist as a faculty member for the program. Therefore, the course could not teach all the subjects in the curriculum.

#### **Collaborative training programs**

The outline of the collaborative training programs is illustrated in Table 1. The NCGM initiated collaborative training with the UHS in the first phase (2017–2019) and the second (2020-2023). During the first phase, the project aimed to support the capacity building of existing pathologists as faculties of the residency program and residents as future pathologists in the country. Since the early 2000s, foreign pathologists from Germany, Japan, and France had been providing support to the pathology departments in hospitals. However, there was no established framework for technical support for this residency program. Lectures were divided among foreign supporters within the in the curriculum. This project began offering lectures in pulmonary and gynecological pathology, along with hands-on training. In 2019, the project initiated its support to the second batch of residents. At the same time, the Technical School for Medical Care (TSMC), an academic institute under the jurisdiction of the UHS, introduced a laboratory technologist bridging course aimed at upgrading the competencies of laboratory technologists and providing them with a bachelor's degree. This project supported

Table 1. Outline of the collaborative training programs

refining the syllabus and developing education materials in local language so that Cambodian pathologists could provide lectures and practice on pathology laboratory in the course.

On average, between 2017 and 2023, Japanese pathology specialists visited Cambodia twice a year to provide lectures and technical advice. The project invited Cambodian pathologists or residents to Japan once a year for training in pathology laboratory management as part of their continuing education. The project continued to provide online lectures and support during the coronavirus disease (COVID-19) pandemic.

During the 7 years of the project, 11 pathology residents completed the course and were certified as pathologists. The pathology education materials for the TSMC course have been developed and are being used by two Cambodian pathologists.

# Challenges in capacity development of pathology professionals in Cambodia

Human resource development requires a systemic approach, which involves a wide range of aspects, from policy and legal inputs to the production, deployment, and retention of health personnel (4). This project focused on production activity only, which is the education of pathologists and pathology technologists.

During the 7 years of activities, the project experienced four critical challenges in the process of developing the pathology education system in Cambodia: *i*) maintaining the quality of lectures and its sustainability, *ii*) maintaining the quality of the practical training environment, *iii*) understanding the barriers to technology application in education, *iv*) consideration of international migration after education. These factors are related to the education process as a pre-service training

Year	Milestones		
2014	<ul> <li>Only 4 Cambodian pathologists were practicing in the country.</li> <li>Pathology services were found to be severely limited due to historical and structural challenges.</li> </ul>		
2015	<ul> <li>First batch of pathology residents enrolled in the newly established UHS residency program.</li> <li>Curriculum developed with international consultation, but lacked sufficient faculty.</li> </ul>		
2017	<ul> <li>NCGM-UHS collaborative project began. (1<sup>st</sup> phase: support for existing pathology workforce).</li> <li>Japanese experts started providing lectures and hands-on training.</li> </ul>		
2019	<ul> <li>1<sup>st</sup> batch of 5 pathology residents graduated from UHS.</li> <li>2<sup>nd</sup> batch of pathology residents enrolled in UHS.</li> </ul>		
2020	• MoU signed between NCGM and UHS (2 <sup>nd</sup> phase: strengthening pathology education system).		
2023	<ul> <li>One graduate from the 1<sup>st</sup> batch appointed as an official lecturer at UHS.</li> <li>Digital slide program introduced to support online education.</li> </ul>		
2024-25	• Three more residents from the 2 <sup>nd</sup> batch appointed as official lecturers at UHS.		

NCGM, National Center for Global Health and Medicine, Japan; UHS, University of Health Science, Cambodia.

#### and deployment of human resources (5).

#### Maintaining the quality of lectures and its sustainability

The first challenge was maintaining the quality of education and sustainability of the educational program. The quality of education heavily relies on the knowledge and skills of the lecturers. However, the capacity development of lecturers takes a long time, especially in a country like Cambodia, where few midcareer pathologists are qualified as lecturers. Bringing pathology specialists from abroad is a quick solution. However, attention should also be paid to develop the capacity of Cambodian pathologists to be lecturers, to ensure sustainability in the long run. In 2017, the NCGM and several Japanese pathologists contributed, covering about 6 subjects and 5-10 h out of 100 h in the curriculum. Pathology specialists from other countries, such as Germany, Switzerland, and Malaysia, also taught the residents. In 2020, the NCGM signed a memorandum of understanding with the UHS to place the capacity building of pathology specialists capable of teaching pathology courses at the university at the core of its activities. Since then, the NCGM, with other coactors, including Japan Society of Pathology and Japan Society of Clinical Cytology have been committed to collaborating (above simply providing lectures) to strengthen Cambodian pathologists' capacity to teach. The project ultimately aimed to ensure that Cambodia's pathology education system would independently provide lectures on its own (6). The NCGM therefore put face-to-face discussions with the UHS dean of the pathology education system at the core of the collaborative activities. As of 2024, 9 years after starting the resident course in 2015, 5 first-batch and 6 second-batch residents have graduated and started their careers as pathologists. Several other Cambodian pathologists were not trained in the resident course but developed their careers outside the country. They started fully contributing to pathology in hospitals and labs in Cambodia. The UHS has set specific requirements for domestic pathologists to be appointed as lecturers in the resident course. Although this initially limited the contribution of Cambodian pathologists to the education system, one graduate of the first-batch resident course, who sufficiently met the requirements set by the UHS, was appointed as an official lecturer in 2023. As of January 2025, three additional graduates from the second batch have been appointed as official lecturers. Several other graduates from the first- and second-batch residencies are now candidates for official lectureship. Although this progress is encouraging, it will still take time before Cambodian lecturers can fully cover the entire residency program.

Maintaining the quality of a practical training environment

The second challenge faced during the project was maintaining the quality of the practical training environment. As the quality of pathology diagnosis is influenced by both pathology slide conditions and pathologists' knowledge, a well-prepared specimen and slide prepared by trained laboratory technologists is a prerequisite to providing accurate pathology diagnosis. Pathology consumables, including various reagents, essential antibodies, and well-maintained laboratory equipment, all contribute to slide quality. However, with an unstable supply chain and the limited market size in Cambodia, local hospitals encountered considerable difficulties in improving the procurement of these consumables. Consequently, pathologists and technologists rarely had enough experience outside the lecture rooms in preparing or evaluating high-quality slides.

## Understanding the barriers to technology application in education

During the COVID-19 period, the project took advantage of technology and online lectures through digital slides. For pathology, online teaching is comparable to faceto-face lectures if digital slides are readily available. However, storing digital slides is a challenge in the realworld setting as it requires responsible local personnel to manage the data and a place for storage (7). In the project, if the UHS, the main body of pathology education, agreed on the importance and advantages of using digital slides in the education system, they would be fully introduced. Like many examples of unused equipment provided by foreign countries, without domestic incentives and commitment to utilizing new equipment, introducing new tools only leads to non-use. In other words, the local initiative can only implement introduction of digital teaching materials and equipment in education through sustainable resource allocation, such as budget and designated personnel. In 2023, the project initiated purchase of a monthly subscription to digital slides, which do not require data storage, for trial use. The project also provided digital teaching materials and ensured that they were used by Cambodian pathologists. During on-site training in Cambodia, the project aimed to have Japanese lecturers supervise them when teaching with the materials.

#### Consideration of international migration after education

Lastly, reflecting common obstacles in any human resource development, the project experienced international migration of the trained workforce. Five first-batch residents started their training. However, after graduation in 2019, only two chose to remain in Cambodia as pathologists, whereas others opted to pursue opportunities abroad. Identifying the factors that cause pathologists to work abroad is beyond the project's scope; however, employment situations could be one of the reasons. Only a few national hospitals in Phnom Penh have pathology laboratories where pathologists can be employed. The environment is also limited in the availability of reagents and necessary consumables, as described previously. Although budgetary allocations for pathology reagents and consumables have improved significantly across hospitals, the lack of procurement routes for some critical reagents and equipment in Cambodia poses ongoing challenges. On a more positive note, preparations for establishing a pathology department at a hospital, which is expected to become the third national cancer center, are underway. This development will expand the domestic recruitment market for pathology professionals in the country. Health workforce development should align with financial and structural input, such as personal remuneration and budgetary support for further capacity development and infrastructural updates (8). Although it may be overly simplistic to attribute the international migration of the trained workforce solely to domestic working conditions, there is a clear need to create an appealing work environment and provide incentives to encourage pathologists to stay and contribute to Cambodia's healthcare system.

On the other hand, the project identified possible opportunities to mobilize pathologists abroad as part of pathology service resources in Cambodia. Notably, online consulting and diagnosis of pathological specimens by Cambodian pathologists abroad have been implemented in certain cases. This setting could be redefined as a global "brain network" (9). With the skills to prepare digital slides, pathologists in Cambodia can connect to Cambodian pathologists working overseas, regardless of the physical distance (10). Moreover, the availability of digital slides and online teaching suggests the possibility of mobilizing those pathologists, who were a part of the brain drain from Cambodia's education system.

In conclusion, the project identified two insights for pathology education toward human resource development: i) fostering the next generation of Cambodian pathologists to take leadership roles in teaching and supporting the education system, and ii) mobilizing pathologists who work overseas as a human resource in pathology education. After 7 years of educational support, several pathologists started contributing to the field of pathology in Cambodia. They have adequate knowledge and experience in pathology, and their experience can be utilized to enrich the education system by employing them as lecturers. Such ongoing professional development and empowerment of young pathologists and laboratory technologists could lay the foundation for establishing academic societies in the future and faculty development at the university. At the same time, the education system in Cambodia needs to be flexible and find a sustainable way to incorporate

young, growing talents in the field of pathology and their contribution into its structure. On a similar note, utilizing Cambodian pathologists abroad can create a breakthrough in the shortage of human resources and pathology capacity. If the pathology education system in Cambodia can effectively collaborate with Cambodian pathologists abroad and incorporate their skills and capacity into the existing services, it will be an excellent resource for future pathology development in Cambodia.

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