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Long-term Survival Outcomes of Prostate Cancer Treated by a Moderately Hypofractionation Regimen (70Gy in 28 fractions): A Single-Center Experience

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ABSTRACT

OBJECTIVE This study aimed to assess the survival outcomes of localized prostate cancer patients treated with moderately hypofractionated radiation therapy (70Gy in 28 fractions).

METHODS Between 2013 and 2018, a total of 96 patients with localized prostate cancer underwent radical radiotherapy. The prescribed dose for the prostate gland was 70Gy delivered in 28 fractions. In cases where elective pelvic lymph node treatment was indicated, the prescribed dose for the elective area was 50.4Gy in 28 fractions. Patient characteristics, dose parameters, treatment outcomes, and toxicities were recorded and analyzed. Treatment results were evaluated following the ASTRO-Phoenix recommendations.

RESULTS Out of the 96 patients, 86 were eligible for evaluation. The average age of the patients was 74 years, with 73 of the 86 patients (84.9%) categorized as high-risk. Eighty-one of the 86 patients (92.2%) received hormonal treatment. With a median follow-up time of 52 months, the 4-year biochemical control, disease-free survival, and overall survival rates were 100%, 100%, and 91.4%, respectively. Among this cohort, three patients experienced grade 3 gastrointestinal (GI) or genitourinary (GU) toxicities.

CONCLUSIONS The results of our study, utilizing 70Gy in 28 fractions for localized prostate cancer treatment, are promising and are comparable to findings reported in other publications. Only three patients in our cohort developed grade 3 or higher toxicity.

KEYWORDS prostate cancer, moderate hypofractionation, survival, outcomes

INTRODUCTION

Prostate cancer is one of the male cancers and is found mostly in high income countries. There are many ways to treat prostate cancer. Selection of treatment is related to stage, initial prostatic specific antigen (PSA), and grade group.

Current treatment options include active surveillance, surgery, radiotherapy, hormonal therapy and focal treatments. In radiotherapy, both external beam radiotherapy (EBRT) and brachytherapy (BT) have a role in the treatment. Presently, EBRT has rapidly improved, reaching

high conformality to target with the technique of intensity-modulated radiation therapy (IMRT) with dose escalation. Based on low alpha/beta ratio, hypofractionation in theory has a role in prostate cancer treatment. Moderate hypofractionation (2.5–5Gy per fraction) has been investigated in many randomized studies and has shown non-inferiority to a dose-escalation regimen (1–3). In cases of moderate hypofractionation, two schedules are the most frequently recommended: 60Gy in 20 fractions and 70Gy in 28 fractions (4). Our hospital implemented a regimen of moderate hypofractionation in 2013 using a 70Gy in 28 fractions that has based on long-term studies by Kupelian et al. (5–7). From then through 2019, more than 90 patients were treated using this regimen. This study evaluated the survival outcomes of patients in our hospital who were treated by 70Gy in 28 fractions.

METHODS

This retrospective study evaluated the survival outcome of prostate cancer patients treated by moderate hypofractionation (70Gy in 28 fractions). The study was approved by the institutional review board (IRB) of the Faculty of Medicine, Chiang Mai University and assigned the study code RAD-2565-09210.

The study evaluated the outcomes of using 70Gy in 28 fractions in prostate cancer patients treated between 2013 through 2018. All patients were at least 18 years old and had a biopsy-proven prostatic adenocarcinoma. No uncontrolled medical conditions were observed and no previous pelvic radiotherapy or surgery was reported for any of the patients.

All patients were treated using the IMRT technique. Simulation was performed using 3-mm slice thickness CT simulation in the supine position with ankle support. Bladder protocol was followed to maintain stable bladder volume during treatment. CT datasets were uploaded to a workstation, then contouring and planning processes were conducted. Clinical target volume (CTV) was composed of prostate gland (and elective pelvic lymph node (LN)). 70Gy in 28 fractions was applied to the prostate gland and 50.4Gy in 28 fractions was applied selectively to the pelvic LN using the simultaneous integrated boost (SIB) technique. The International Commission on Radiation Units and Measurements report 83 (ICRU 83) was followed to evaluate the dose to targets. **Figure 1** shows images used in planning this study.

After completion of treatment, patients were scheduled for follow-up by PSA and physical examination. In the first 2 years, every 3–6

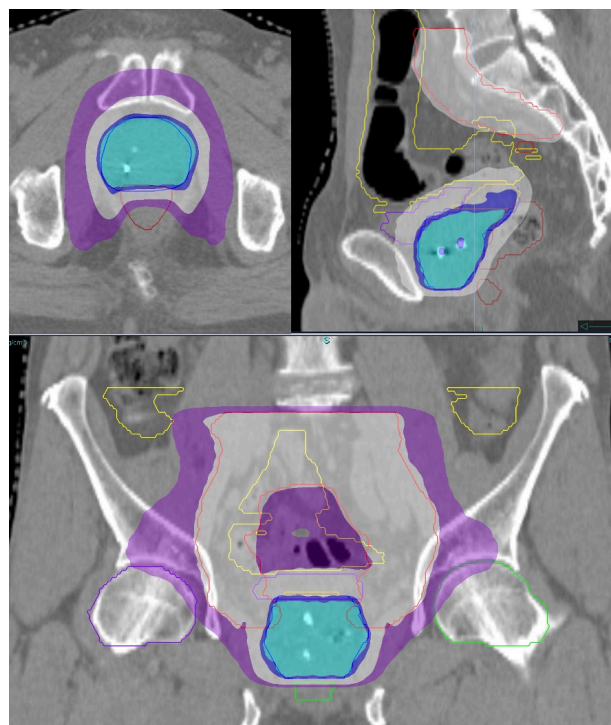


Figure 1. Dose distribution of 70Gy in 28 fractions (marine blue = 70 Gy; light yellow = 50.4 Gy)

months were designed and during 3rd-5th year, every 6 months were designed. For the first two years, examinations were scheduled every 3 to 6 months, then every 6 months during the 3rd to 5th years. ASTRO-Phoenix recommendations (nadir +2 ng/mL of PSA value) were used to evaluate the biochemical recurrence after radiotherapy (8). Overall survival is defined as the status from the start of treatment to death. Descriptive statistics are used to evaluate the quantitative data. SPSS version 22 was used for statistical evaluation.

Table 1. Patient characteristic data

Parameters	Details
Age	74 years (range 50-93)
Initial PSA	57.4 ng/mL (range 2.4-406)
PSA value	
Up to 20 ng/mL	41(47.7%)
More than 20 ng/mL	45(52.3%)
Gleason score	
Less than 6	19 (22.1%)
7	17 (19.7%)
8-10	50 (59.2%)
Tumor stage	
T1	2 (2.3%)
T2	35(40.7%)
T3	36 (41.9%)
T4	13 (15.1%)
Risk group	
Low risk	1 (1.2%)
Intermediate risk	12 (13.9%)
High risk	73 (84.9%)
Elective nodal treatment	
Yes	74 (86%)
No	12 (14%)
Androgen deprivation treatment	
No	5 (5.8%)
Short-term treatment	8 (9.3%)
Long-term treatment	73 (84.9%)
Treatment Technique	
Helical TomoTherapy	52 (60.5%)
Volumetric-modulated arc therapy	34 (39.5%)

PSA, prostatic specific antigen; ng/mL, nanograms per millimeter

Table 3. Late toxicities

Parameters	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Cystitis (GU)	79 (91.9%)	4 (4.6%)	1 (1.2%)	2 (2.3%)	0
Proctitis (GI)	83 (96.5%)	0	2 (2.3%)	1 (1.2%)	0

GI, gastrointestinal; GU, genitourinary

RESULTS

From 2013 to 2018, 96 patients were treated in our hospital. Of those, 10 patients were excluded due to missing data; the remaining 86 patients were evaluated. The mean age of the evaluated patients was 74 years. The most common Gleason Score was 8-10 and the median PSA value was 21ng/ml. Seventy-four patients were treated by combined pelvic LN irradiation. Patient characteristics are shown in [Table 1](#).

The mean dose to the target (D50 of PTV) was 70.7Gy. The mean dose to the D10% of the bladder and rectum were 67.9Gy and 64.7Gy, respectively. The median total treatment time was 41 days. [Table 2](#) shows the dose characteristics for the cohort.

With a median follow-up time of 52 months, 20 patients died, 4 patients had biochemical recurrence and 3 patients had distant metastasis. The 4-year biochemical control, progression-free survival, and overall survival rates were 100%, 100%, and 91.8%, respectively. During this period, 10 patients experienced toxicity events. Three patients had grade 3-4 toxicity. Details of toxicity are shown in [Table 3](#).

Table 2. Dose characteristic data

Parameters	Details (mean ± SD)
Volume of PTV prostate	129 cc (range 57 cc-358 cc)
D50 of PTV	70.7±0.7Gy
D98 of PTV	67.2±1Gy
D2 of PTV	72.6±1.1Gy
D10 bladder	67.9±2.7Gy
D15 bladder	65.5±4.3Gy
D25 bladder	60.7±5.9Gy
D50 bladder	49.9±7.9Gy
D10 rectum	64.7±4.5Gy
D15 rectum	61.5±5.3Gy
D25 rectum	55.8±6.3Gy
D50 rectum	44.4±7.2Gy
D50 penile bulb	32.1±14.6Gy
D5 right head of femur	30.7±7.7Gy
D5 left head of femur	30.5±8.1Gy

Dx, dose as a percentage of volume; Gy, gray; PTV, planning target volume; SD, standard deviation

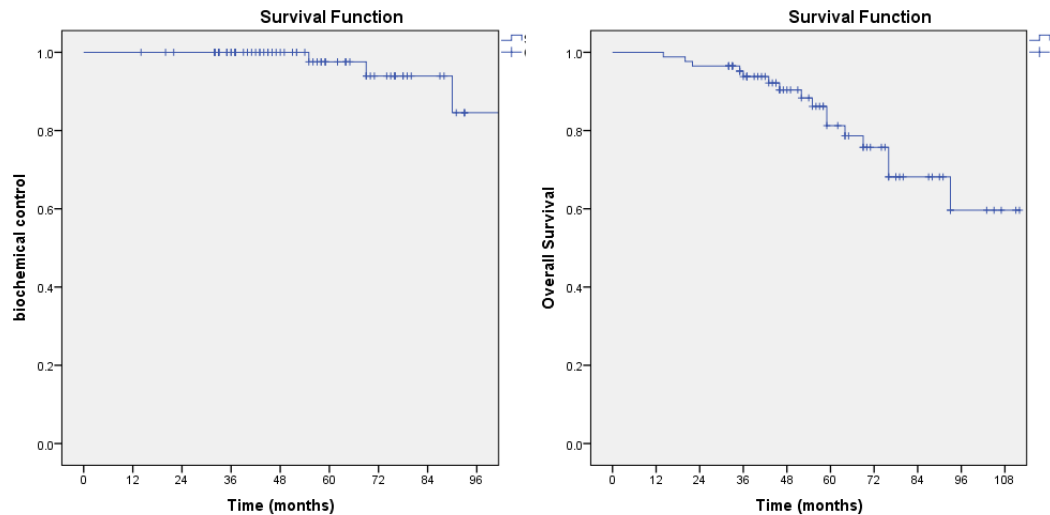


Figure 2. Kaplan-Meier survival curve of Biochemical Control and Overall Survival

DISCUSSION

Radiotherapy is one option for treatment of localized prostate cancer. Recently, moderately hypofractionated radiotherapy has come to be the standard treatment for localized prostate cancer based on randomized controlled studies showing non-inferiority results in comparisons with a dose-escalated conventional regimen. Presently, the schedules of 70Gy in 28 fractions and 60Gy in 20 fractions are supported internationally (9).

The regimen of 70Gy in 28 fractions was initially introduced by Kupelian, et al. in 2001 (6,10,11). This regimen is supported for utilization in all-risk localized prostate cancer. Ten-year results of 70Gy in 28 fractions was published in 2019. Those results showed the 10-year biochemical relapse-free survival rates were 88% for low risk, 78% for favorable intermediate risk, 71% unfavorable intermediate risk, and 42% for high-risk patients. For all patients, the 10-year actuarial overall survival rate was 69% (95% confidence interval, range 66%–73%) (12). Table 4 shows the results of selected studies of moderately hypo-fractionated regimens for localized prostate cancer. Our study reported the results of treatment of prostate cancer in our center with 70Gy in 28 fractions. The 4-year biochemical relapse-free survival and overall survival rates in our analysis were 100%, and 91.8%, respectively. These results are comparable to a study by Kupelian et al. which reported a 5-year biochemical relapse-free survival rate of 88% (6). Results of

our study are closest to those in a study by Kim et al. which also used 70Gy in 28 fractions) (13).

Our study had some limitations. First, the number of patients in the study was small (86 patients) due to the low number of prostate cancer patients receiving radical radiotherapy at our hospital during the period 2013–2018. Second, our study has shorter follow-up time than some other international publications. Third, this study used a retrospective approach. Finally, the follow-up program was disrupted by the COVID-19 outbreak. Notwithstanding, our study reported the results of a moderately hypo-fractionated regimen on localized prostate cancer of various risk levels (especially high risk). In our analysis, the 4-year b-RFS and OS rates were 100% and 91.8%, respectively, results comparable to other studies with the same schedule (6,13).

CONCLUSIONS

Use of 70Gy in 28 fractions for localized prostate cancer treatment is promising, with results comparable to previous reports and only three patients developing grade 3 or higher toxicity.

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Table 4. Selected studies of moderately hypo-fractionated regimens

Study	N	Patients	FU	RT schedule	Results	Toxicity
CHHiP (1)	3,216	pT1b-T3aNoMo, prostate cancer	62.4 mos.	Group I: 74Gy in 37Fx Group II: 60Gy in 20Fx Group III: 57Gy in 19Fx	5-yr. biochemical or clinical failure-free survival rate Group I: 88.3% Group II: 90.6% Group III: 85.9%	Gr2+ GI and GU Group I:13.7% and 9.1% Group II:11.9% and 11.7% Group III: 11.3% and 6.6%
RTOG 0415 (2)	1092	Low prostate cancer risk group	5.8 yrs.	73.8Gy in 41fx vs.70Gy in 28fx	5-yr. DFS 85.3% in the conventional arm and 86.3% in the hypo-fractionated arm	Late grade 2 and 3 GI and genitourinary adverse events were increased (HR, 1.31 to 1.59) in patients who were treated with H-RT.
HYPRO (14,15)	820	Stage T1b-T4 NoMo, iPSA up to 60ng/mL,	60 mos.	64.6Gy in 19fx vs. 78Gy in 39fx	5-yr. RFS was 80.5% for hypo-fractionated arm and 77.1% for conventional arm	G3+GI 17.7% vs. 21.9% (NS) G3+GU 39.0% vs. 41.3%(NS)
Abu-Gheida et al. (12)	834	LR 266, IR 344, HR 244	11.3 yrs.	70Gy in 28 fractions	10-yr. OS 69%	Gr3+ GU or GI 2% and 1%, respectively.
Kupelien et al. (6)	100	LR36 IR30 HR34	66 mos.	70Gy in 28Fx	5 yr. b-RFs 88%	Gr3+GI 3% Gr3+GU 1%
Kim et al. (13)	30	LR 5 IR 5 HR 20	74.4 mos.	70Gy in 28Fx	5 yr. b-RFS 92.9% in hypo-fractionated arm	Gr2+GU 3.3% Gr2+GU 6.6%
Our study	86	LR 1 IR 12 HR 73	52 mos.	70Gy in 28Fx	4-yr. b-RFS 100% 4-yr. OS 91.8%	Gr2+GU 3.5% Gr2+GI 3.5%

GI, gastrointestinal; GU, genitourinary; Fx, fraction; HR, high risk; IR, intermediate risk; iPSA, initial PSA before treatment; LR, low risk; FU, follow-up; mos, months; OS, overall survival; b-RFS, biochemical relapse-free survival; WHO, World Health Organization

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ADDITIONAL INFORMATION

Contribution

E.T.: concept design, data grouping, data calculation, data analysis, and manuscript writing; P.M.: data collection, S.C.: data collection; P.K.: data collection, WO: data collection,

B.J.: data collection; P.T.: data collection; W.N.: physics data collection; A.W.: physics data collection; I.C., V.S, and V.L.: consultant. This manuscript was reviewed by all authors.

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CT and MRI Manifestations of IgG4-Related Disease in the Abdomen: A Retrospective Review

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ABSTRACT

OBJECTIVE IgG4-RD is an immune-mediated systemic inflammatory disease that affects multiple organs, including in abdomen and pelvis, and presents with various radiologic appearances. The purpose of this study was to review the imaging manifestations of IgG4-RD in the abdomen at Siriraj hospital.

METHODS This retrospective study was approved by the IRB of Siriraj hospital. Thirty-five patients diagnosed with IgG4-RD with abdominal involvement in the 17-year period 2003-2020 identified by searching hospital radiology and ICD10 data bases were included. Thirty-three CT and three MRI images, including one patient with a CT at the initial presentation and an MRI at a relapse presentation, were reviewed by a radiologist for the presence of organ involvement.

RESULTS A total of 105 abdominal problems were identified among the 35 patients, with many patients having more than one issue. The most common issue was pancreatitis which was diagnosed in 22 patients (62.9%), followed by bile duct in 18 patients (51.4%), retroperitoneum in 16 patients (45.7%) and kidney in 16 patients (45.7%). A minority of patients also had rare liver, mesentery, prostate gland and/or urethral involvement. Various features in each organ were described and characterized.

CONCLUSIONS IgG4-related disease in the abdomen or pelvis can present a wide spectrum of clinical and imaging findings. Recognizing the relevant imaging features facilitates the establishment of an effective diagnosis as well as the differentiation of this disease from other benign or malignant conditions.

KEYWORDS IgG4-related disease, IgG4-related disease in abdomen, IgG4-related disease in pelvis, abdominal involvement of IgG4-related disease, autoimmune pancreatitis, multifocal fibrosclerosis

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated, chronic relapsing-remitting inflammatory condition characterized by infiltration of IgG4-positive plasma

cells and lymphocytes with associated fibrosis, causing mass-forming lesions within one or more affected organs. Most patients have an increasing level of serum IgG4 (1). The disease was firstly reported in 2001 in a type 1 autoimmune

pancreatitis patient, and was recognized as systemic disease in 2003 (2). The criteria for diagnosis of IgG4-RD developed by a Japanese group in 2011 (1) includes clinical characteristic diffuse or localized swelling or masses in one or more organs, elevated serum IgG4 concentrations (≥ 135 mg/dL) and histopathologic examination showing marked lymphoplasmacytic infiltration and storiform fibrosis (3). IgG4-RD is one of a small number of diseases for which there is still no data regarding prevalence. The estimated incidence in Japan is around 0.28–1.08/100,000 population (4). The multisystem and organ involvement, however, has been

categorized in a number of publications as described in Table 1 which shows radiologic findings of IgG4-RD manifestations in the abdomen and pelvis, including pancreas, bile ducts, gallbladder, liver, retroperitoneum (fibrosis), kidney, and prostate gland.

According to the Japanese criteria, the radiologic characteristics of these organ involvements play an important role in IgG4-RD diagnosis (4). Some of the radiologic findings, however, resemble malignancy, especially the mass-forming pattern in involved organs. Better understanding of these lesions would facilitate the establishment of a more effective strategy for confirming the

Table 1. Radiologic findings of IgG4-RD intra-abdominal manifestation (4–6)

Organs and disease	CT	MRI
Pancreas Type 1 autoimmune pancreatitis - Diffuse disease - Focal disease	Non-contrast enhanced CT (NCECT): Hypoattenuation (4) CE: Delayed enhancement pattern due to the presence of parenchymal fibrosis, capsule-like rim or halo of low attenuation surrounding the pancreas (4) CT, MRCP, ERCP: Diffuse or segmental narrowing of the main pancreatic duct and sometimes stenosis of the bile duct, duct penetrating sign, ice pick sign, absent or mild upstream dilatation of the pancreatic duct (4) Rare findings: calcifications, pseudocyst, severe peripancreatic stranding	T1: Hypointense T2: Mildly hyperintense DWI: Restriction (significantly lower than that of pancreatic cancer) (5)
Liver and Bile duct IgG4-related sclerosing cholangitis	MRCP, ERCP: Focal or diffuse bile duct wall thickening, mostly associated with stenosis and upstream dilatation A circular and symmetric ring of tissue encasing the bile duct wall, with relatively smooth margins and homogeneous enhancement in the delayed phase	
Gallbladder	Diffuse acalculous cholecystitis (5)	
IgG4-related inflammatory hepatic pseudotumor	Homogeneous delayed enhancement	T1: Hypointense T2: Hyperintense CE: Variable
Kidney - Tubulointerstitial nephritis (TIN) - Chronic sclerosing pyelitis - Inflammatory pseudotumor of the ureter	IgG4-TIN CECT: bilateral, hypodense lesions 1. Bilateral round or wedge-shaped peripheral cortical lesions (the most common) 2. Diffuse patchy involvement 3. Rim of soft tissue around the kidney 4. Bilateral nodules in the renal sinuses 5. Diffuse wall thickening of the renal pelvis (6)	T1, T2: low signal intensity GE: mild enhancement
Prostate Prostatitis	Prostate gland enlargement with or without focal lesion (5)	
Retroperitoneum	A soft-tissue mass, covering the abdominal aorta and its branches (4) with or without aortitis	
Mesentery sclerosing mesenteritis	Soft-tissue mass enveloping the mesenteric vessels, preservation of fat around vessels, "fat ring sign", specks of calcification (20% of the cases) (4)	
Nodes	<2 cm lymphadenopathy mostly at the hilar region (5)	

diagnosis and to institute the appropriate treatment. To that end, this study reviewed imaging findings from CT and MRI scans of the abdomen and pelvis of IgG4-RD patients recorded in Siriraj Hospital.

METHODS

Patients

Patients diagnosed with IgG4-RD in Siriraj Hospital between 1 April 2003 and 31 January 2020 were identified. The study cohort was identified from the institution's radiology database using the searching terms "IgG4" and "IgG4-RD" as well as recognized conditions in the spectrum of IgG4-RD (1,5,6), e.g., autoimmune pancreatitis (AIP), mass-forming pancreatitis, Kuttner's tumor, Mikulicz's disease, sclerosing sialadenitis, sclerosing cholangitis, sclerosing dacryoadenitis, inflammatory pseudotumor, periaortitis, periarteritis, retroperitoneal fibrosis, interstitial nephritis, inflammatory abdominal aneurysm, and multifocal fibrosclerosis, in radiological reports including clinical summaries, imaging findings, diagnoses, and impressions. Additional searches were conducted of the ICD 10 database for the code D803 which indicates the presence of IgG4-RD.

Inclusion criteria

The inclusion criteria used for the diagnosis of IgG4-RD in this study (4) were histology-proven IgG4-RD (including morphological characteristics of typical storiform fibrosis and/or obliterative phlebitis, an increased absolute number of IgG4⁺ plasma cells, and an elevated IgG4⁺/IgG⁺ plasma cell ratio) (7) or a diagnosis by clinicians of involvement of IgG4-RD in one or more organs with elevated serum IgG4 (>135 mg/dL) (5). For example, type 1 autoimmune pancreatitis (AIP) and IgG4-RD pancreatitis do not always require histological confirmation, rather the diagnosis is based on clinical features and specific imaging features of pancreatic manifestations (Table 1) with elevated IgG4 serum. All patients included in this study had undergone abdominal CT or MRI scanning in Siriraj Hospital at the time of diagnosis.

Clinical features

Electronically stored clinical notes for all patients were retrospectively reviewed for

gender, age, past medical history, clinical presentation, and course of treatment. The serum IgG4 level (mg/dL) at the time of diagnosis was also obtained.

Statistics

Data was analyzed using Predictive Analytics Software 18.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis was performed using descriptive statistics (mean, standard deviation, and percentage).

CT and MRI examinations

Of the 35 patients, 33 had undergone CT scanning of the abdomen at the time of presentation. The scanning protocols were varied, with coverage of the scan categorized as whole abdomen (19 cases) or upper abdomen (14 cases). One patient underwent a non-contrast CT scan due to poor renal function. Three patients underwent MR imaging of the abdomen (2 upper abdomen with MRCP and 1 lower abdomen). One patient underwent CT and MRI scanning of the lower abdomen at the time of the first and second new organ presentation, respectively.

The CT and MR images of the patients were retrospectively reviewed for organ involvement by an abdominal radiologist. The number of lesions, laterality, maximal diameter of the lesion in centimeters, location, shape (round or wedge shaped), border, attenuation for CT or signal intensity for MR imaging (hypo- or hyper-attenuation of signal intensity of the lesion compared with the adjacent normal parenchyma of that organ), focal (limited to one part of the organ) or diffuse (throughout the whole organ) involvement and mass effect of the lesions were analyzed separately for each organ.

Ethical approval

This retrospective study was approved by the Siriraj Institutional Review Board of Siriraj Hospital NO. Si 716/2020.

RESULTS

Patients

By reviewing the clinical data, imaging, and histology of the patients identified by the database search, 35 cases of IgG4-RD that met the inclusion criteria were finally identified. Of the 35 patients, 21 (60%) had histology-proven

IgG4-RD (10 from an intra-abdominal organ, 12 extra-abdominal). An additional 14 patients (40%) were diagnosed as having possible IgG4-RD based on the Japanese Comprehensive Clinical Diagnostic (CCD) criteria for IgG4-RD using the clinical evaluation and IgG4 level.

The majority of the patients were more than 50 years old, with a male-female ratio of 4:1. The majority of the cohort had a clinical presentation (97%). The symptoms were attributed to jaundice in 12 patients (34.3%), while 10 patients (28.6%) had nonspecific abdominal symptoms such as chronic abdominal pain and epigastric pain. Seven (20.0%) presented with a mass in the head and neck region. Other clinical presentations included weight loss (n=2, 5.8%), acute kidney injury (n=1, 2.9%), pleural effusion (n=1, 2.9%), and prolonged fever (n=1, 2.9%). One patient was incidentally found to have IgG4-RD in the form of retroperitoneal fibrosis during surveillance of alcoholic cirrhosis.

Other medical diseases of the study cohort were type 2 diabetes mellitus (9 patients), chronic viral hepatitis (2 patients), and prior malignancy (5 patients: 2 prostate cancers, 1 thyroid cancer and 2 hematologic malignancies). One patient was found to have Hashimoto thyroiditis.

Organ manifestations

Among the 35 patients, a total of 105 abdominal imaging manifestations were identified at the time of diagnosis. The pancreas was the most frequently affected organ, involved in 22 cases (62.9%), with a majority (14 cases) presenting in a diffuse form. This was followed by bile duct involvement in 18 patients (51.4%), with an even distribution between focal and diffuse forms. Kidney and retroperitoneal involvement were each seen in 16 patients (45.7%), with the kidney cases split between parenchymal and non-parenchymal involvement, while all retroperitoneal cases exhibited periaortitis and 5 also had additional areas of involvement in the retroperitoneal space. Gallbladder involvement was observed in 10 patients (28.6%), all of whom had diffuse wall thickening. Mesenteric involvement occurred in 7 patients (20.0%), all presenting with mass formation, and the same number had lymph node involvement characterized by enlarged nodes

with homogeneous density. Liver involvement was noted in 4 patients (11.4%), primarily in a diffuse form. The least common were prostatic and urethral involvements, each seen in only one patient (2.9%), both exhibiting in a diffuse form (Tables 2 and 3).

DISCUSSION

IgG4-RD is a chronic inflammatory disease that can affect multiple organs, including head and neck, thorax, abdominal area and pelvis as well as skin. The most common presentation is a mass-like lesion or soft tissue infiltration that mimics neoplasm.

The study population was mostly late middle age to elderhood with males predominating. The findings of this study resemble a study of 235 cases of IgG4-RD in Japan by Inoue et al. (8). The initial clinical presentations of the patients in this study were abdominal-related or extra abdominal-related (head and neck, thorax) symptoms and non-specific symptoms (weight loss and fever). Around 1/3 of the cohort had a non-abdominal-related presentation with intra-abdominal involvement discovered by imaging. This is concordant with a prior study which stated that in many cases involvement of other organs is asymptomatic and can only be found by comprehensive imaging of the chest and abdomen (9). Thus, performing a thorough imaging, including the abdomen, is necessary for assessment of disease at the time of diagnosis.

This study presents the abdominal imaging findings in IgG4-RD cases. The majority of those cases involved more than one abdominal organ. The pancreas was the most commonly involved organ, followed by the bile duct, retroperitoneum and kidney, findings similar to a study by Inoue et al. (8), where involvement of the pancreas, kidney, bile duct and retroperitoneum were found in 60%, 23%, 13%, and 4% of cases, respectively.

Only 3 patients (8.6%) in this study had isolated organ involvement in the pancreas, retroperitoneum, and kidney, fewer than that in studies by Okazaki et al. (10) and Inoue et al. (8) which reported single organ involvement in approximately 10-20% and 42% of patients, respectively. The remaining 32 patients (91.4%) in the current study had multiple organ manifestations, both intra- and extra-abdominal.

Table 2. Patient data including age, sex, IgG4 level, extra-abdominal organ involvement, diagnosis and imaging modality at presentation

Patient data	n (%)
Age (years)	Mean 63.89 [IQR 58-70]
IgG4 level (mg/dL)	median 1,290.00
Sex	2
- Male	8 (80.0)
- Female	7 (20.0)
Extra abdominal organ involvement	
- Salivary gland	9 (25.8)
- Orbital pseudotumor	5 (14.3)
- Lung	4 (11.4)
Japanese Comprehensive Clinical Diagnostic criteria (4)	
- Definitive: Pathology + Clinicals/Imagings + IgG4 level	21 (60.0)
- Possible: Clinicals/Imagings+IgG4 level	14 (40.0)
Imaging at modality at clinical presentation	
- CT	32 (91.4)
- MRI	2 (5.7)
- CT and MRI	1 (2.9)
Organ involvement	
- Pancreas	22 (62.9)
- Bile duct	18 (51.4)
- Kidney	16 (45.7)
- Retroperitoneum	16 (45.7)
- Gallbladder	10 (28.6)
- Mesentery	7 (20.0)
- Lymph nodes	7 (20.0)
- Liver	4 (11.4)
- Prostate gland	1 (2.9)
- Urethra	1 (2.9)

Table 3. Image findings of abdominal organ involvement

Organ involvement	Number (%)		
Pancreatic involvement	22 (62.9)	Focal form (8)	Diffuse form (14)
Bile duct involvement	18 (51.4)	Focal form (9)	Diffuse form (9)
Tenal involvement	16 (45.7)	Parenchymal involvement (9)	Non-parenchymal involvement (7)
Retroperitoneal involvement	16 (45.7)	Periaortitis (16)	Periaortitis and other areas of retroperitoneal space (5)
GB involvement	10 (28.6)	Diffuse wall thickening (10)	
Mesenteric involvement	7 (20.0)	Mass formation (7)	
Lymph nodes	7 (20.0)	Enlargement, homogeneous density nodes (7)	
Liver involvement	4 (11.4)	Focal form (1)	Diffuse form (3)
Prostatic involvement	1 (2.9)	Diffuse form	
Urethral involvement	1 (2.9)	Diffuse form	

Most patients had multi-organ involvement at the time of initial diagnosis. One patient had known IgG4-RD in multiple organs including pancreas, retroperitoneum, kidney, liver and gallbladder. The clinical status of remission in that individual was followed by chronic persistent disease and the patient subsequently presented with a periurethral mass seven years after the initial diagnosis.

In the group with multi-organ involvement, some multiple abdominal organ involvement had been found. Bile duct involvement was found with pancreas or gallbladder involvement in 63.6% and 90% of cases, respectively. Renal involvement with retroperitoneal involvement and lymph node enlargement was found in 56.3% and 71.4% of patients, respectively. Almost half the patients (n=15, 42.8%) had extra-abdo-

minal involvement including the head and neck (sialadenitis and orbital pseudotumor) and thorax (pleural effusion, lung nodules, consolidation and mediastinal lymphadenopathy).

Abdominal manifestation

Pancreatic involvement

Pancreatic involvement was found in 22 patients. Four patients who were suspected of having a pancreatic mass subsequently underwent surgery with result of finding IgG4-related pancreatitis. Fourteen patients (63.6%) had a diffuse form of pancreatic involvement which appeared as a diffuse enlargement and loss of pancreatic lobulation or as a diffuse pattern (Fig. 1A). Eight patients (36.3%) had a focal form of pancreatic involvement (head=5, body=2 and tail=1). The proportion of these patterns was similar to that in another study which reported diffused enlargement among 11%–56% and focal or mass-like enlargement among 28%–59% of patients (11). In another series, a ‘mixed’ appearance of diffuse and focal enlargement was found in 56% of patients (12). However, no clear examples of the mixed form were found in the present study and only one case of diffuse enlargement with the predominating area at the head, neck or uncinete pro-

cess was depicted.

Most CT scans of the affected pancreatic parenchyma showed hypoenhancement or delayed/late enhancement, whereas normal enhancement was found in only 2 patients. Of the 2 patients with MR images, pancreatic parenchyma was slightly diffuse hypointense on T1-weighted MR images and hypointense on T2-weighted MR images in addition to restricted diffusion. Normal gadolinium enhancement was observed and no pancreatic duct involvement was identified. Christoph et al. described late enhancement, a classical finding of autoimmune pancreatitis, in 25% of patients with CT scans and 74% of patients with MRI (12). The restricted diffusion was possibly an indication of active disease (13).

Additional instances of diffuse patterns were found frequently, e.g., peripancreatic fat stranding (n=5, 35.7%) and a capsule like rim around the pancreas (rim halo sign) (n=8, 57.1%). This capsule-like rim around pancreas was found in a greater proportion (57.1%) of cases in this study than in other studies (25–40%) (14). Other features were less frequent seen, e.g., focal peripancreatic fluid (n=1, 0.07%) and multiloculated cystic lesion at the tail of the pancreas (n=1, 0.07%). Three patients (21.4%)



Figure 1. Pancreas and bile duct involvement A. IgG4-related pancreatitis, diffuse pancreatic involvement (arrow) B. IgG4-related pancreatitis, diffuse pancreatic enlargement and multiloculated cyst or probably wall-off necrosis at tail of pancreas (arrow) and distal CBD narrowing (arrowheads) C, D. IgG4-related cholangitis, CBD wall thickening (arrowheads)

were suspected of having splenic vein thrombosis. Multiloculated cystic lesion (Fig. 1B) can be found in case reports of autoimmune pancreatitis (15). For one patient in the present study, underlying chronic alcoholic disease was cited. Despite the high serum IgG4 levels and CT images which revealed diffuse pancreatic and distal common bile duct (CBD) involvement, the nature of this cystic lesion was still uncertain due to the lack of a definitive biopsy. Other probable co-existing diagnoses were alcoholic chronic pancreatitis with pancreatic pseudocyst and pancreatic cystic neoplasm.

In this study, the pancreatic duct was not a significant imaging feature for detection in either CT or MRI, e.g., pancreatic dilatation and duct penetrating sign, probably due to limitations of the CT imaging protocol or to the small number of MRIs in the study. In the case of the diffuse form of IgG4-RD pancreatitis, less visualization of the pancreatic duct was noted and it was presumed to be an indication of extrinsic ductal narrowing secondary to peri-ductal edema or inflammation.

Bile duct involvement

Of the 18 patients with bile duct involvement, 16 underwent CT scans and 2 had MRI scans. Those are not the investigations of choice for patients with biliary involvement (16). Other findings were identified as diffuse involvement (n=9, 50.0%) and focal involvement (n=9, 50%). The majority of the findings were compatible with common features of sclerosing cholangitis, i.e., smooth bile duct wall thickening (Figs. 1C, 1D) as well as progressive enhancement and variable luminal narrowing. Focal involvement appeared as focal smooth wall thickening of the bile duct and various segments of the biliary tract including the entire extrahepatic bile duct (EHD) in 6 patients (66.7%) and in one patient with distal CBD, confluence of the intrahepatic bile duct (IHD) and multifocal short segments involving the IHD and EHD. One focal form showed infiltrated soft tissue lesions or mass-forming involving the hepatic duct confluence and proximal CBD causing upstream dilatation, resembling malignancy such as infiltrative hilar cholangiocarcinoma (17).

Renal involvement

Of the 16 patients with renal involvement (all CT scans), 9 patients (56.3%) had renal

parenchymal involvement and 7 (43.7%) had perirenal, renal sinus, or renal pelvis. This finding differs from one study that reported a much greater proportion of parenchymal involvement (75% of 48 cases) (6). One patient with pathologically proven IgG4-related tubulointerstitial nephritis had only a non-contrast CT scan, which revealed nonvisualized lesions. Almost all patients (n=13) had bilateral involvement. Only two patients were found to have unilateral involvement where in both patients the lesions were seen in the right kidney.

Renal parenchymal lesions had the same variation in patterns reported in other studies, most of which were identified as well-defined multiple wedge- or round-shaped cortical lesions (n=6), less commonly as multiple small (subcentimeter) peripheral cortical nodules (n=2) and rarely as diffused patchy infiltration (n=1). On CT scans, the renal parenchymal lesions were low attenuation areas compared with the normal renal cortex during the first and the delayed enhancement phases. None of the lesions were visible on non-enhanced CT scans. Two patients with cortical involvement were found to have perirenal fat stranding. Still, most of the findings were found to have many differential diagnostic considerations. For instance, multiple wedge- or round-shaped cortical lesions (Fig. 2A) had indications of pyelonephritis (18) and vascular insults. Other diseases that also have bilateral renal hypodense lesions, especially metastasis and lymphoma, should be identified in the differential diagnosis, as should other renal inflammatory diseases such as Wegener's granulomatosis (19). A perirenal soft tissue thickening or soft tissue rim sign (Fig. 2B) was also found in one patient where the images resemble lymphoma, retroperitoneal fibrosis, and Erdheim-Chester disease (20).

Patterns of renal involvement of other than the parenchyma were also observed. One patient had irregular enhancement of soft tissues in the bilateral renal sinuses with adjacent fat stranding (Fig. 2C). Diffuse wall thickening of the renal pelvis (Fig. 2D), similar to those reported in another study (6), was present in eight patients. Six of these patients had renal pelvic wall thickening extending to the ureter. No hydronephrosis was seen. One study (6) reported renal pelvic wall involvement without

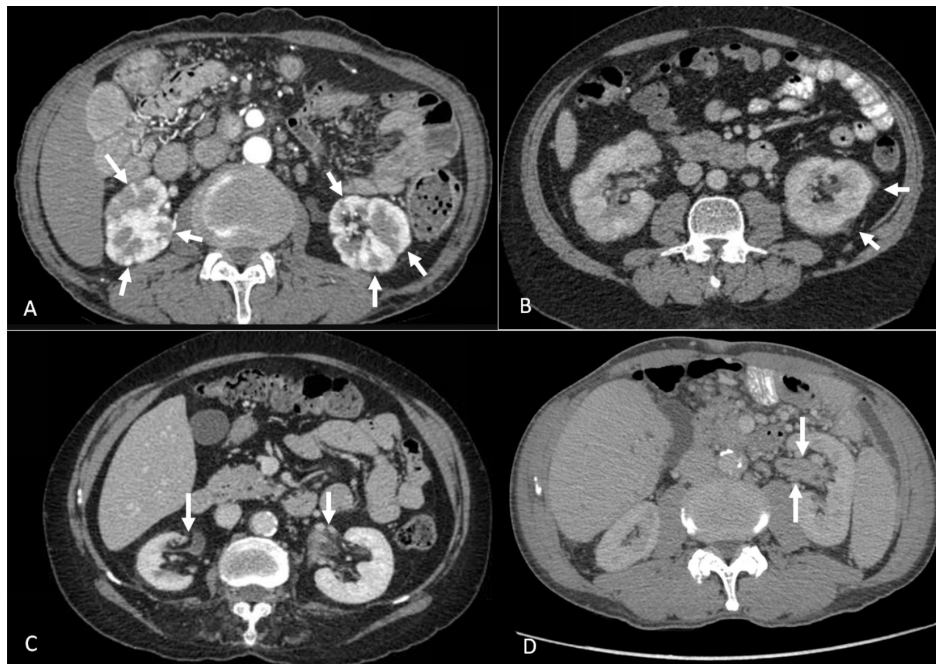


Figure 2. Axial CT images from different patients show renal involvement A. Wedge-shaped peripheral cortical lesions (arrows), B. Diffuse patchy parenchymal involvement with perinephric hypodense soft tissue (arrows) C. Ill-defined soft tissue at renal sinus (arrows), D. Diffuse wall thickening of the renal pelvis (arrows)

retroperitoneal fibrosis and that mild hydronephrosis was observed in about 10% of cases. In cases of marked renal pelvis wall thickening, a differential diagnosis of other infiltrative diseases, e.g., pyeloureteritis and urothelial neoplasms, including infiltrative transitional cell carcinoma, should be considered (21).

Three patients demonstrated two patterns of involvement at initial presentation, either diffuse renal pelvis wall thickening together with patterns of cortical nodules or diffuse patchy and soft tissue at the renal sinus which could indicate the possibility of coexisting lesions in this disease.

Retroperitoneal involvement

All 16 patients with retroperitoneal lesions were visualized as having soft tissue characteristically surrounding the infrarenal part of the abdominal aorta and/or the iliac arteries classical features of retroperitoneal fibrosis which is also called IgG4-related periaortitis (4,22). Five patients had other areas of soft tissue formation within various regions of the retroperitoneum including the posterior pararenal space (n=1), the presacral space (n=1), the renal pelvis (n=2) and the paracaval region (n=1).

The locations of aortic involvement were mostly the infrarenal aorta to the proximal common iliac artery (15 patients), while one

patient also had a short-segmented lesion at the origin level of the renal artery. All the lesions were asymmetrical circumferential soft tissue thickening with progressive delayed enhancement (Fig 3A). The average maximal thickness was 0.7 cm (range 0.5 to 1.8 cm). There was mild dilatation of the affected aorta in 1 patient (about 2.5 cm at the infrarenal aorta), while the rest of the patients had a normal diameter aorta. A varied degree of calcified plaques in the affected aorta was visualized in 12 patients. These findings are similar to those reported in a study of 22 patients by Dai et al. (22). However, a few divergences from that study were noted, e.g., a slightly lower average maximal thickness of the lesions in the present study (mean 0.7 cm compared to 11 mm) and significantly less luminal involvement with mild dilatation of the aorta which was found in only one case compared to 7 of 22 cases in another study (22). One patient in this study with aortic ectasia (IgG4-related pancreatitis and periaortitis) was a 76-year-old man who had underlying diseases including cardiovascular disease and hypertension, so in this case, the aortic ectasia might be related to aging and underlying diseases more than to IgG4-RD luminal involvement. Additionally, three patients with soft tissue formation at the paracaval and presacral

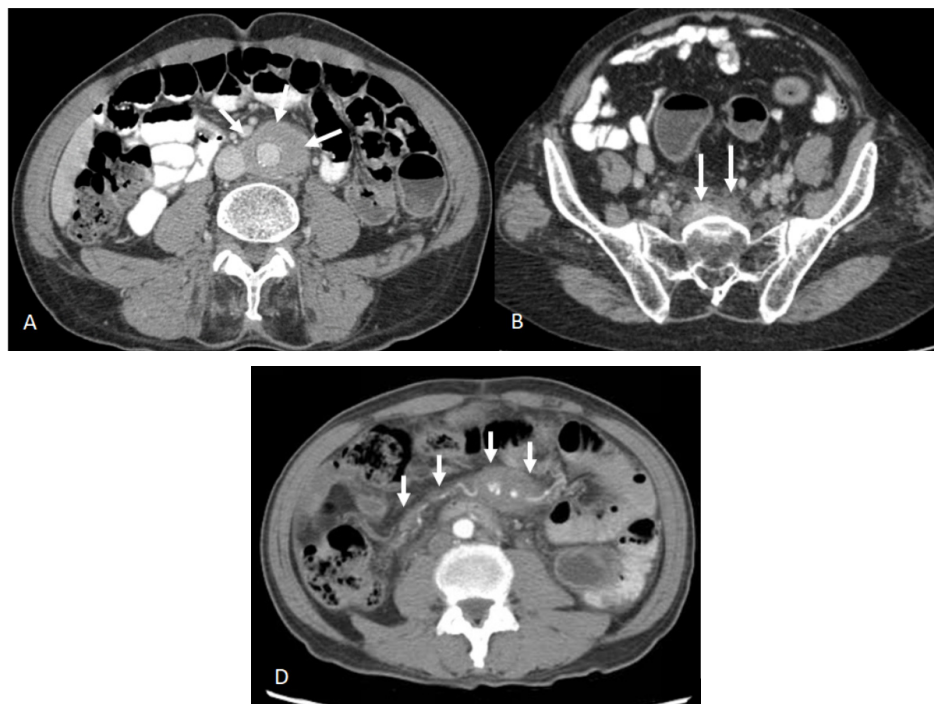


Figure 3. Axial CT images of retroperitoneum and mesenteric involvement A. Periaortic soft tissue density or periaortitis (arrow), B. Soft tissue thickening at presacral region (arrow), C. Soft tissue thickening around mesenteric vessels (arrow)

region (Fig. 3B) and the renal pelvis had bilateral proximal peri-ureteric soft tissue thickening without hydronephrosis or hydroureter.

Other intra-abdominal organ involvement. Other less frequent intra-abdominal organ involvements were found in this study, including gallbladder, mesentery, liver, prostate gland and urethra. Diffused gallbladder wall thickening was visualized in 10 patients of whom only one patient had pericholecystic fat stranding. This feature cannot be differentiated from other cause of chronic cholecystitis. However, 90% of the cases of gallbladder involvement were associated with bile duct involvement as well. It is possible that the accompanying evidence of bile duct involvement could be important for diagnosis.

Mesenteric involvement was found in 7 patients. The lesions were characterized by fat stranding and enhancing soft tissue formation at the mid abdomen, enveloping the mesenteric vessels including the superior mesenteric artery (n=6) and the inferior mesenteric artery (n=1) (Fig. 3C), which is characteristic of sclerosing mesenteritis (4). Peritoneal thickening was found in 3 patients, although several conditions can mimic this appearance in CT scans including lymphoma, carcinoid tumor, carcinomatosis,

primary mesenteric mesothelioma, and mesenteric edema (23).

Liver parenchymal lesions were visualized in 4 patients. The lesions were described as a large, ill-defined wedge-shaped area involving the entire hepatic lobe, with heterogenous enhancement in 3 patients. Another patient was found to have an ill-defined hypodense mass which was associated with mild IHD dilatation (Fig. 4A), however, that is non-specific and could be described as infiltrative liver neoplasm (24).

Intra-abdominal lymph node enlargement (greater than 1 cm in the short axis) was found in 7 patients. The enlarged lymph nodes were found in various regions, mostly at the paraaortic and mesenteric regions. Most of the lymph nodes had an oval shape and homogeneous density with a size less than 2 cm. These findings could be nonspecific, but may represent an inflammatory process related to IgG4-RD (4). This study had a limitation in complete nodal evaluation because of the lack of pathology-proven evaluation of the lymph nodes, so the lymph node enlargement could have been a reactive node resulting from a chronic disease.

Prostatic involvement was pathologically proven in one patient with IgG4-RD of the salivary gland and lacrimal gland. The CT revealed



Figure 4. IgG4-RD from different patients with liver, prostate gland and urethral involvement A. Inflammatory pseudotumor at liver, the ill-defined mass with delayed enhancement (arrows), B. IgG4-related prostatitis, generalized prostate enlargement and no focal lesion (arrow), C. IgG4-related pseudotumor at urethra, the circumferential peri-urethral soft tissue mass with hypo T2 signal intensity, homogeneous faint enhancement and restricted diffusion (arrows)

an enlarged prostate gland with homogenous enhancement (Fig. 4B). No focal lesion was noted. The serum prostatic surface antigen (PSA) at that time was 6.59 ng/dL. The patient had a lower urinary tract symptom and underwent transurethral resection of the prostate (TURP). However, this CT finding could also be visualized in other prostatitis, including infection, and should be differentiated from malignancy.

An IgG4-related pseudotumor at the urethra visualized in one patient was pathologically proven to be a lesion resulting from a chronic persistent disease over many years and a newly developed urethral lesion. The MR scan of this lesion revealed an oval bulging mass at the urinary bladder neck and membranous urethra which showed homogenous intermediate signal intensity on a T1W image, hypointensity on T2W images, homogenous enhancement and restricted diffusion (Fig. 4C). The appearances are similar to those found in another case

report (25). However, those imaging findings also overlap with those of malignant tumors such as urethral neoplasm (26).

Finally, the study showed that IgG4-related disease in the abdomen mainly reveals multi-organ involvement at the initial presentation. One patient can have multi-organ involvement in different time frames. Some subtle radiographic findings or lesions are tumor-like mimics. Typical features are a homogeneous pattern and faint or delayed enhancement on both CT and MRI and hypointensity on T2W MR images. The restricted diffusion on MRI is probably indicative of an active disease. A limitation of this study is the lack of pathologic evaluation of other associated abnormal lesions. However, due to the characteristically excellent response of IgG4 to steroid therapy, follow-up imaging might be helpful for making a more complete diagnosis during post treatment evaluation.

CONCLUSIONS

IgG4-related disease in the abdomen and pelvis presents a wide spectrum of clinical and imaging findings, and may affect many different organs in different ways. Diagnosis requires maintaining a high degree of suspicion. Definitive diagnosis should be based on pathologic, laboratory and radiologic findings. It is also important that the radiologist recognize imaging features in order to effectively establish an accurate diagnosis which leads to appropriate management.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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Associations Between BMI, Serum Hormone Levels, Time Since Ovarian Insufficiency Onset, Serologic Autoimmunity, and Prevalence of Common Parameters: A cross-sectional Retrospective Study of Premature Ovarian Insufficiency

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ABSTRACT

OBJECTIVE Premature ovarian insufficiency (POI) affects 1:100 women before the age of 40. The objectives include exploring correlations between body mass index, years since the onset of premature ovarian insufficiency, follicular stimulating hormone, and estradiol; and studying prevalence of five common serologic autoimmunologic parameters during POI diagnosis.

METHODS The records of idiopathic POI patients presenting with secondary amenorrhea who visited the Gynecologic Endocrinology Unit, Siriraj Hospital, between January 1, 2000 and December 31, 2016 were reviewed. Extracted data included body mass index, years since premature ovarian insufficiency onset, levels of follicular stimulating hormone and estradiol. Five common serologic autoimmunologic parameters were also retrieved where available.

RESULTS Among the 161 idiopathic POI patients analyzed, a significant reverse correlation was found between serum follicular stimulating hormone and estradiol ($r=-0.209$, $p=0.008$), while no correlations were identified between body mass index, years since the onset of premature ovarian insufficiency, and serum estradiol ($p=0.141$, $p=0.240$, respectively). After excluding cases with abnormal karyotypes which can potentially cause POI, the remaining 146 cases was comprised of 72 cases with a normal 46,XX karyotype (the first group) and 74 cases who declined karyotype investigation (the second group). At least one of the serologic autoimmunologic parameters was investigated in 43 cases in the first group and in 20 cases in the second group. Anti-nuclear antibody was the most prevalent in the first group (25.0%) while anti-thyroglobulin was the most prevalent in the second group (30.7%).

CONCLUSIONS Only serum follicular stimulating hormone and estradiol exhibited significant reverse correlation in POI cases with secondary amenorrhea. Baseline serologic autoimmunologic parameters were positive but didn't indicate autoimmune diseases during POI diagnosis.

KEYWORDS premature ovarian insufficiency, body mass index, years since premature ovarian insufficiency, follicular stimulating hormone, estradiol, serologic autoimmunologic parameters

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INTRODUCTION

Premature ovarian insufficiency (POI) is defined as a premature cessation of ovarian function before the age of 40. It is an important etiology of deficiency in many sex steroids found in reproductive-aged women globally. When POI occurs after menarche, a patient usually presents with prior irregular menstrual cycles with or without menopausal symptoms or with secondary amenorrhea (SA). It is estimated that POI affects 1:100 women by the age of 40, 1:1,000 women by age 30, and 1:10,000 by the age of 20 (1-5). An increased level of follicular stimulating hormone (FSH) in a menopausal range and a low estradiol (E2) level, also defined as a hypergonadotropic hypogonadism state, are characteristics of this condition.

Androstenedione is the main steroid produced and secreted by postmenopausal ovaries and the level is about one-half of that before menopause (6). Estrone (E1) is produced mainly by the peripheral aromatization of androstenedione mostly in adipose tissue and then is continuously converted to E2 (7). The body mass index (BMI) has been hypothesized to finally affect E2 levels after menopause. One previous study of surgically menopausal women who were younger than naturally menopausal women assumed that extra-gonadal site estrogen production started approximately 12-18 months later in the surgically menopausal women compared with natural menopause (8). This is hypothesized to occur after POI since the POI patients are much younger than the naturally menopausal women. However, to date studies of correlations between BMI, years since premature ovarian insufficiency (YSP) and serum E2 of POI patients have been limited and in most cases the results reported were from mixed types of menopause.

Previously reported etiologies of POI are heterogeneous. Many advanced clinical investigations have attempted to identify additional etiologies of POI. Despite this effort, the cause of POI in the majority of cases remains unknown and idiopathic cases are reported in 74%-90% of POI patients (9,10). Known potential causes include identifiable underlying diseases, e.g., genetic diseases, chromosome abnormalities, autoimmune diseases, or iatrogenic causes such as previous chemotherapy or radiation

therapy. Autoimmune diseases have been reported to be the cause of POI in 4-30% of cases, with the strongest association being with thyroid diseases (11-15). Nevertheless, many autoimmune antibodies have been reported to be prevalent at baseline in both POI cases with a normal 46,XX karyotype without clinical autoimmune diseases and in normal women controls (16).

The primary objectives of the present study were to study the correlations between body mass index (BMI), serum follicular stimulating hormone (FSH) level, years since premature ovarian insufficiency (YSP) and serum estradiol (E2) level in idiopathic POI patients presenting with secondary amenorrhea. The secondary objective was to study the prevalence of five common serologic autoimmunologic parameters (SAPs) at the time of POI diagnosis.

METHODS

This cross-sectional retrospective study was conducted at a single tertiary-care hospital in Bangkok, Thailand. The study was approved by the Siriraj Ethical Committee on Research Involving Human Subject (SiRB No. 609/2020). Informed consent was exempted as this was a retrospective study. However, permission to use the patients' electronic data in this study was approved by the Director of Siriraj Hospital. The records of patients who presented with SA, were idiopathic POI at diagnosis, and who were seen at the Gynecologic Endocrinology Unit, Faculty of Medicine Siriraj Hospital between 1 January 2000 and 31 December 2016 were reviewed. The inclusion criteria were: patients with available and complete electronic medical records, age < 40 years at the time of POI diagnosis, presented with SA \geq 4 months without any hormonal treatment given during that time, and with serum FSH levels \geq 40 mIU/mL on two occasions at least one month apart. The exclusion criteria were: patients with previous bilateral oophorectomy, a history of mumps oophoritis, previous chemotherapy affecting ovarian function, radiation therapy at the pelvic or the abdominal area, known autoimmune diseases, e.g., Hashimoto's thyroiditis, systemic lupus erythematosus, autoimmune polyglandular syndrome, at the time of POI diagnosis, or other known underlying diseases or conditions

which can cause POI, e.g., acquired immunodeficiency syndrome and heavy smoking. The flow chart for POI patient selection in this study is shown in Figure 1.

Patient data extracted included age at menarche, age at last menstrual period, age at registration at the hospital, duration of SA, YSP (calculated as full calendar years since the last menstrual period), serum FSH and E2 levels at the time of POI diagnosis, weight and height, body mass index (BMI) calculated as weight in kg divided by height in meter squared, and the results of five common SAPs where available.

Sample size calculation

As the correlation between the BMI and the serum E2 level of the POI patients was not available, the sample size was calculated based on a previous report of mixed menopausal cases who had been seen at the Gynecologic Endocrinology Unit, Faculty of Medicine, Siriraj Hospital. The correlation between the BMI and the serum E2 was found to be 0.27 (17). Based on an $r = 0.27$, $\alpha = 0.05$ (two-sided test), and $\beta = 0.1$, it was determined that a total of 140 cases were needed. An additional 21 cases (15%) were added for a total of 161 consecutive cases identified without selection bias were finally enrolled. The last case included in the study was registered with the hospital in December 2016.

Serum FSH and serum E2 assays

Serum FSH and serum E2 assays were performed by the electrochemiluminescence immunoassay method (ECLIA) (Elecsys, Roche Diagnostics, Germany) at the Clinical Pathology Department, Faculty of Medicine, Siriraj Hospital. The sensitivity of the assay for FSH was 0.3 mIU/mL with inter- and intra-assay coefficients of variation of 5% and 5.2%, respectively. The sensitivity of the assay for E2 was 5 pg/mL, with both inter- and intra-assay coefficients of variation of 5%.

Autoimmune assays

The five common SAPs investigated in this study were as follows:

1. Rheumatoid factor (RF): RF was studied using the immunoturbidimetric assay. The results were reported as < 15.0 U/mL = negative, $15.0-25.0$ U/mL = borderline and > 25.0 U/mL = positive. The test was performed to investigate for rheumatoid arthritis.

2. Anti-nuclear antibody (ANA): ANA was studied using the indirect immunofluorescence (IIF) method. The results were reported as Negative, Borderline or Positive based on the titer and pattern. The test was performed to investigate for systemic lupus erythematosus (SLE) and other connective tissue diseases.

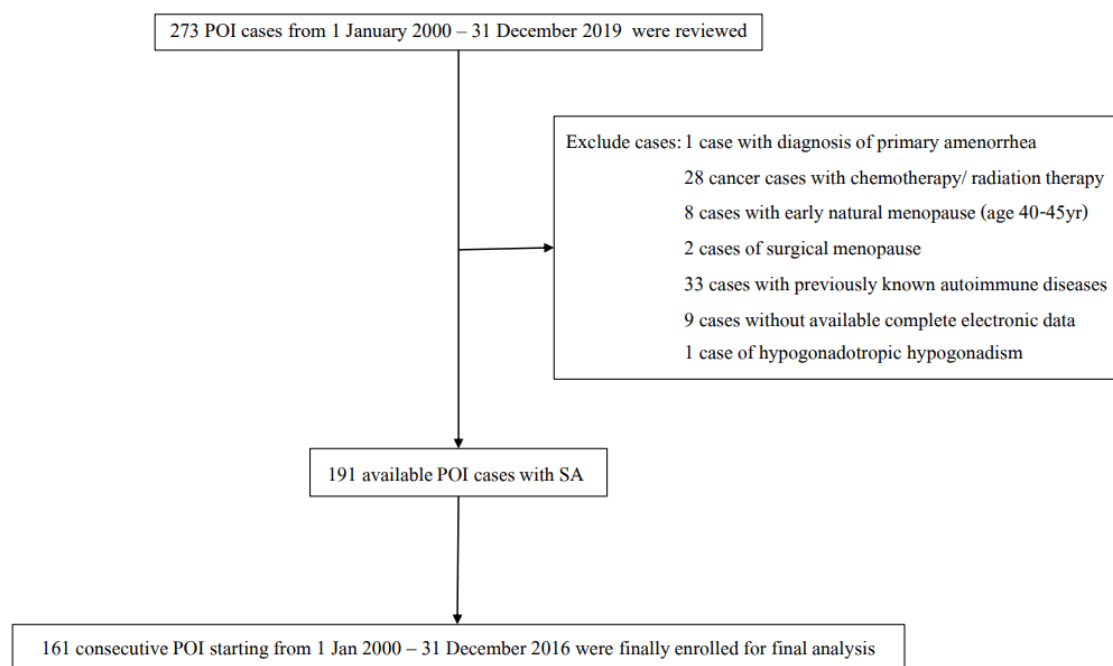


Figure 1. Flow diagram of patient selection in this study

3. Anti-doublestranded DNA (Anti-dsDNA): Anti-dsDNA was studied using the IIF method. The results were reported as negative, borderline or positive together with the titer. The test was performed to investigate for SLE.

4. Anti-thyroperoxidase antibody (Anti-TPO): Anti-TPO was studied using the electrochemiluminescent immunoassay (ECLIA) method. The results were reported as: ≤ 34 IU/mL = negative, $> 34-65$ IU/mL = borderline and > 65 IU/mL = positive. The test was performed to investigate for Hashimoto's thyroiditis and autoimmune thyroiditis.

5. Anti-thyroglobulin: Anti-thyroglobulin was studied using the chemiluminescent microparticle immunoassay (CMIA) method. The results were reported as: < 35 IU/mL = negative and ≤ 35 IU/mL = positive. The test was performed to investigate for Hashimoto's thyroiditis and autoimmune thyroiditis.

Statistical analysis

Descriptive quantitative data are presented as number, percentage, and mean \pm SD, where appropriate. The t-test was used to compare the baseline clinical characteristics between the normal karyotype group and the group with no karyotype investigation. Pearson's correlation was used to determine the correlations between BMI, serum FSH, YSP and serum E2. The Statistics Package for the Social Science Program (SPSS 18.0 statistical package (IBM Corp. in Armonk, NY) was used for data analysis. *P*-values < 0.05 were considered statistically significant.

RESULTS

All the initial 161 patients had been newly diagnosed with POI and were sporadic cases. The baseline clinical characteristics of the cases in this study are shown in [Table 1](#). POI diagnosis was made at or before age 30 years in 29.2% of the cases. The most delayed diagnosis was made 10 years after the onset of SA. The correlations between the FSH, BMI, YSP and serum E2 of the 161 cases are summarized in [Table 2](#). There was a significant reverse correlation between the serum FSH and the serum E2 ($r = -0.209$, $p = 0.008$). The correlations between both the BMI and YSP with serum E2 were not statistically significant ($p = 0.141$ and $p = 0.240$,

Table 1. Baseline characteristics and laboratory results of the 161 cases enrolled in this study

Baseline characteristics of patients	POI cases (n = 161)
Age at POI (mean \pm SD, yr)	32.48 \pm 6.15
Age at registration (mean \pm SD, yr)	35.08 \pm 6.84
Duration of SA (mean \pm SD, yr)	2.32 \pm 2.53
Age at menarche (mean \pm SD, yr)	14.32 \pm 2.27
Gravidity (mean \pm SD)	0.66 \pm 1.09
Parity (mean \pm SD)	0.58 \pm 0.95
Abortion (mean \pm SD)	0.07 \pm 0.32
Weight (mean \pm SD, kg)	53.78 \pm 8.71
Height (mean \pm SD, cm)	155.46 \pm 5.96
BMI (mean \pm SD, kg/m ²)	22.32 \pm 3.91
Serum FSH (mean \pm SD, mIU/mL)	92.10 \pm 37.09
Serum E2 (mean \pm SD, pg/mL)	16.36 \pm 16.61

Table 2. Correlations between the FSH, BMI, years since premature ovarian insufficiency (YSP) and E2 of all 161 cases in this study

Pearson correlation	E2
FSH Correlation Coefficient	-0.209
<i>p</i> -value	0.008*
BMI Correlation Coefficient	-0.116
<i>p</i> -value	0.141
YSP Correlation Coefficient	-0.093
<i>p</i> -value	0.240

*Statistically significant

respectively). [Figures 2A, 2B and 2C](#) show scatterplots of the serum FSH, BMI, YSP and serum E2.

A karyotype study was offered to all 161 patients, but was accepted by only 87 cases. After karyotype investigation, 15 of the 87 cases (17%) were found to have abnormal karyotypes, possibly causing POI (data not shown in the present study). Of the remaining 146 patients, 72 (49%) had a normal 46,XX karyotype and 74 (51%) did not undergo karyotype investigation. The baseline clinical characteristics of the 72 normal 46,XX karyotype cases and the 74 cases who did not undergo karyotype investigation are shown in [Table 3](#). The mean age at POI, age at registration and duration of SA were all significantly lower in the group with a normal karyotype than in the group without a karyotype investigation ($p = 0.001$, 0.001 and 0.010 , respectively).

Investigation of the five common SAPs was performed in 63 of the 146 patients. Of those, 43 cases with a normal karyotype (59.7%) and 20

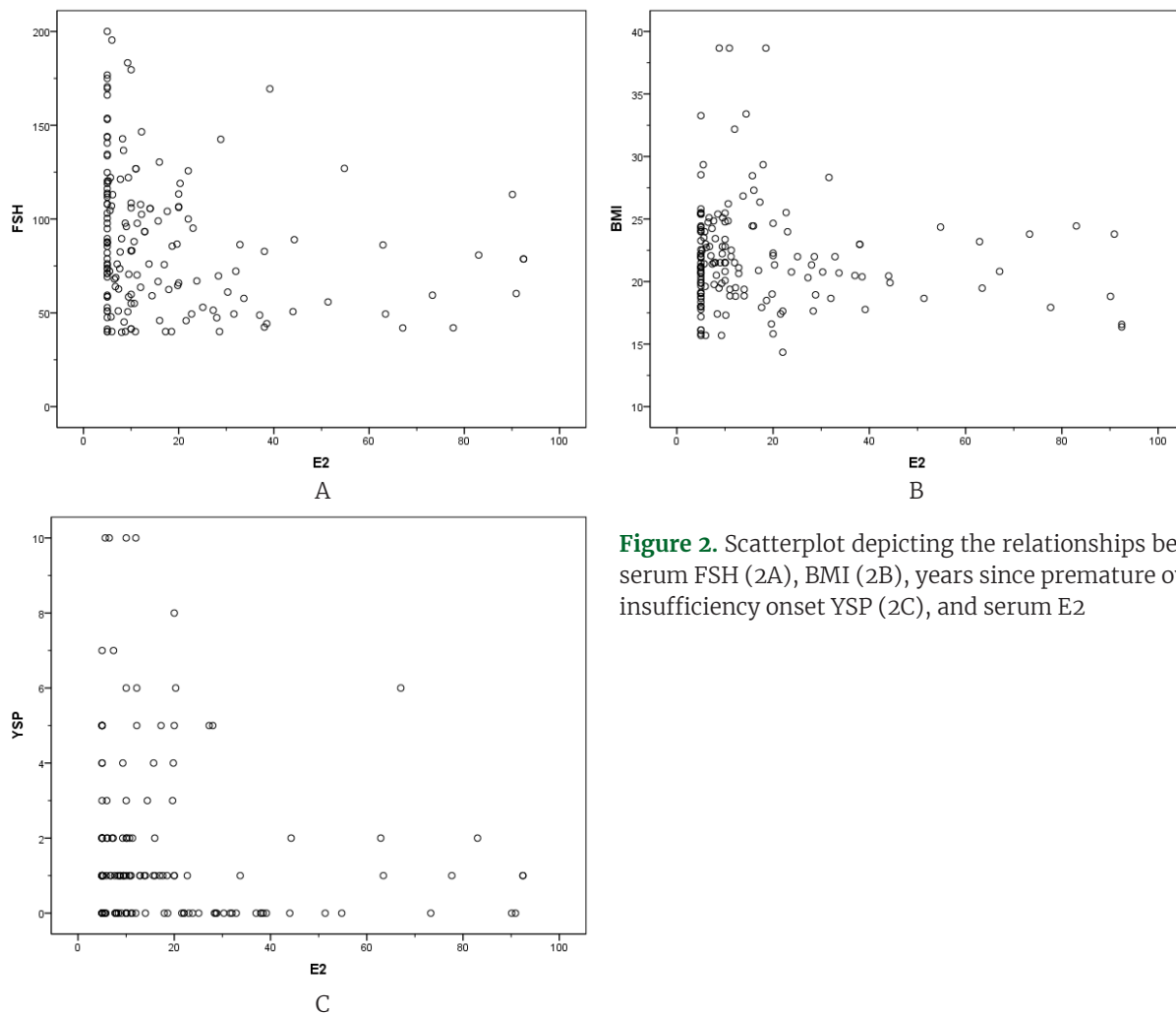


Figure 2. Scatterplot depicting the relationships between serum FSH (2A), BMI (2B), years since premature ovarian insufficiency onset YSP (2C), and serum E2

Table 3. Baseline characteristics of the 72 cases with a normal karyotype and 74 cases without a karyotype investigation in this study

Baseline characteristics of patients	POI with a normal karyotype (n=72 cases)	POI without a karyotype study (n=74 cases)	p-value
Age at POI (mean±SD, yr)	30.72±6.23	35.45±3.94	0.001*
Age at registration (mean±SD, yr)	32.72±7.06	38.43±4.53	0.001*
Duration of SA (mean±SD, yr)	1.74±2.07	2.64±2.56	0.010*
Age at menarche (mean±SD, yr)	14.05±2.23	13.75±2.72	0.428
Gravidity (mean±SD)	0.56±1.00	0.85±1.22	0.099
Parity (mean±SD)	0.46±0.85	0.77±1.08	0.060
Abortion (mean±SD)	0.08±0.36	0.08±0.32	0.785
Weight (mean±SD, kg)	52.29±7.77	54.09±8.67	0.201
Height (mean±SD, cm)	156.00±6.34	154.55±4.81	0.175
BMI (mean±SD, kg/m ²)	21.51±3.11	22.71±4.01	0.124
Serum FSH (mean±SD, mIU/mL)	97.11±39.42	88.48±32.33	0.264
Serum E2 (mean±SD, pg/mL)	16.28±19.48	16.92±14.60	0.324

*Statistically significant

cases in the without a karyotype study (27.0%) had at least one of the five common SAPs investigated. As shown in Table 4, anti-dsDNA was negative in all the cases investigated in the

normal karyotype group whereas RF and anti-dsDNA were negative in all the cases without a karyotype study. The most prevalent positive antibody in the first group was for ANA (40/43

Table 4. Prevalence of five serologic autoimmunologic parameters of 63 POI patients

SAPs	Cases with a normal karyotype and at least 1 SAP studied (Total number = 43 cases)			Cases without karyotype investigation and with at least 1 SAP studied (Total number = 20 cases)		
	No. of cases studied (%)	Results	% Prevalence	No. of cases studied (%)	Results	% Prevalence
1. RF	30 (68.1)	N = 25/30 B = 3/30 P = 2/30	83.3 10.0 6.6	10 (50.0)	N = 10/10 B = 0 P = 0	100.0 0 0
2. ANA	40 (90.9)	N = 27/40 B = 3/40 P = 10/40	67.5 7.5 25.0	12 (60.0)	N = 9/12 B = 2/12 P = 1/12	75.0 16.6 8.3
3. Anti-dsDNA	31 (70.4)	N = 31/31 B = 0 P = 0	100.0 0 0	13 (65.0)	N = 13/13 B = 0 P = 0	100.0 0 0
4. Anti-TPO	24 (54.5)	N = 21/24 B = 0 P = 3/24	87.5 0 12.5	10 (50.0)	N = 8/10 B = 0 P = 2/10	80.0 0 20.0
5. Anti-thyroglobulin	31 (70.4)	N = 26/31 P = 5/31	83.8 16.1	13 (65.0)	N = 9/13 P = 4/13	69.2 30.7

RF, rheumatoid factor; ANA, antinuclear antibody; Anti-dsDNA, anti-double stranded deoxyribonucleic acid; Anti-TPO, anti-thyropoxidase; N, normal; B, borderline; P, positive

cases = 25.0%) and the most prevalent positive antibody in the second group was for anti-thyroglobulin (4/13 studied cases = 30.7%), respectively. Nevertheless, at a three-year follow-up, only one case in the normal karyotype group had developed autoimmune thyroiditis. This patient did not initially undergo RF investigation and was negative for all the other four antibodies. At the three-year follow-up, anti-thyroglobulin in that patient was positive with a level of 112.3 IU/mL. None of the cases in the second group had clinical autoimmune disease at the end of the third year.

DISCUSSION

The results of the present study show a reverse correlation between the serum FSH and serum E2, but no significant correlations between the BMI, YSP and serum E2 were observed. However, no previous study of POI patients only from Thailand was available for comparison. As previously mentioned, an increase in serum FSH and a decrease in serum E2 are characteristics of menopause. These findings have been reported to be influenced by ethnic differences (18). A later study reported that obese postmenopausal women had significantly lower serum FSH compared to overweight and normal weight women (19). The number of subjects

in the present study was too small to compare the results with that report. The same results might be expected in both POI patients and women with natural menopause since both groups have intact ovaries, although the age of the POI group is undoubtedly younger.

After natural menopause, which occurs at approximately age 50 in Thai women (20), the ovaries cease producing many sex steroids, in particular, E2. The mean E2 level starts to decline two years before the final menstrual period, decreases rapidly after menopause and then plateaus (21). Also, the relationship between the BMI and the percentage of body fat by body composition analysis have been reported to be different across ethnic groups and to vary between Asian and White populations. It has also been reported that urban Thais, young Japanese, Hong Kong Chinese, Singaporean and Indonesian women have lower BMIs when compared with Europeans with a similar percentage of body fat (22). In one previous study of natural menopausal women, statistically significant positive correlations between the ideal body weight as well as serum E1 and serum E2 were reported (6). A later study also showed a significant positive correlation between the BMI and the serum E2 level (21). Another study reported that obese postmenopausal women

had significantly higher E2 levels compared to overweight or normal-weight women, and concluded that obesity is an important factor affecting hormone dynamics, but without a clear mechanism (19). Conversely, in another study of natural menopause at a six-year follow-up no correlation between the BMI and the log E2 was observed (23). Due to the relatively small number of patients in the present study, subgroups of our patients by weight were not compared. The results of this research also support the hypothesis that POI ovaries have the same pathophysiology for sex steroid production after cessation of ovarian function in the same fashion as cases of natural menopause. In the present study, YSP did not show a significant correlation with serum E2. This might be explained by the observation that the serum E2, after a rapid decline in levels since POI, plateaus in the same way as in natural menopause.

In the present study, the mean age at POI, mean age at registration with the hospital and duration of SA were all significantly lower in the group with a normal karyotype. This could be explained by the fact that these cases were younger patients, mostly before their third decade of life. They had been adequately informed of the risk of possessing the Y chromosome or Y-chromosome sequences for which early prophylactic gonadectomy is strongly recommended to prevent a possible germ cell tumor later in life. This type of tumor can be found in one or both gonads in 30% of cases, usually before the age of 30 (24). Therefore, more of the younger POI patients had decided to undergo karyotype investigation as they knew the importance of this investigation.

In idiopathic POI, evidence suggesting an autoimmune involvement is weak (25). The antibodies investigated in the present study were comprised, both organ-specific and non-organ-specific types. POI resulting from autoimmunity, although most strongly associated with thyroid disorders, is at increased risk of occurring in cases of adrenal insufficiency, myasthenia gravis, rheumatoid arthritis, SLE, etc (26). The five common SAPs studied were chosen for the detection of common autoimmune diseases. Positive results for the antibodies investigated in this study among the normal karyo-

type patients were also described in a report of Chinese POI patients. In that report, the prevalence in POI patients was significantly higher than in the normal controls, although both groups had no clinical autoimmune diseases (16). The prevalence of the antibodies investigated in the present study are shown in Table 4. Some of the SAPs in this study (RF, ANA, anti-dsDNA) were the same as in the Chinese report, although a lower number of SAPs were investigated in the present study. Interestingly, ANA, a non-organ specific autoantibody, was reported to be positive in 42%–77% of cases among POI patients with a normal karyotype in one study although without clinical significance (27). Anti-TPO, which was investigated for thyroid autoimmunity, has been previously reported to be positive in 14.6% of healthy women in the United States National Health and Nutrition Examination Survey (NHANES III) (28). Anti-TPO was also later reported to be positive in 24.1% of the POI women, significantly higher than the 9% of the healthy controls (29). Nevertheless, the European Society of Human Reproduction and Embryology guideline in 2016 recommended anti-TPO screening for all POI women (30).

From the results of this study, screening for common SAPs is not routinely recommended due to the high false positive rates. Only one case in the normal karyotype group of the present study whose RF was not studied at baseline and for whom the results of the other four SAPs were initially negative, developed autoimmune thyroiditis by the the third-year follow-up. This finding suggests the importance of the correlation between positive SAPs and the subsequent occurrence of autoimmune diseases, an area that needs further exploration. This study also found some positive SAPs results at baseline among patients without a karyotype study, but without clinical significance. A longer follow-up time of all cases might show the clinical significance of autoimmunity.

Strengths and limitations

The strengths of this study include that all the initial 161 cases were idiopathic at the time of POI diagnosis and were without clinical autoimmune diseases. Also, the patients were

consecutively enrolled without a clinical bias. All the patients were Thai and so were expected to possess similar adipose tissue aromatase activity without ethnic variation. The hormonal assays and the SAPs investigated were performed at the same laboratory. All the cases were accessed and followed-up via electronic data. False-positive common SAPs have not been previously reported among Thai POI patients presenting with SA who possess a normal karyotype.

As this was a retrospective study, there were inevitably some limitations. For instance, the number of patients was relatively small. All the five common SAPs were not performed with every patient. Also, other SAPs related to other autoimmune diseases, e.g., anti-ovarian antibodies, were not investigated, so the true prevalence of relevant SAPs was not determined. More complete investigations, including additional SAPs, should be performed and a larger number of patients need to be studied.

CONCLUSIONS

In the present study, among idiopathic POI patients presenting with SA the serum FSH was significantly inversely correlated with serum E2, whereas BMI and YSP were not correlated with serum E2. Baseline positive SAPs were not correlated with autoimmune diseases at the time of POI diagnosis. However, these positive SAPs might play a role in causing autoimmune diseases later in life. Karyotyping should be the first investigation for POI etiology in Thai patients presenting with SA. If normal, then extensive investigation of SAPs might be conducted.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest related to this research.

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None.

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Incidence, Risk Factors, and Clinical Outcomes of Reintubation Following Planned Extubation in a Postanesthetic Care Unit: A Case-control Study

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ABSTRACT

OBJECTIVE This study aimed to determine the incidence, risk factors, and clinical outcomes associated with reintubation after a planned extubation (RAP) during the postoperative period.

METHODS A retrospective case-control study was conducted on patients with RAP in an operating theater or postanesthetic care unit. Forty-six cases between 2013 and 2017 were extracted from the anesthetic database of the Department of Anesthesiology, Faculty of Medicine, Chiang Mai University. Cases with RAP were randomly matched in a ratio of 1:4 with selected controls. Univariable and multivariable logistic regression were used for the analysis and results are presented as the odds ratio (OR) and 95% confidence interval (CI).

RESULTS A total of 230 patients (46 cases and 184 controls) were included. The independent risk factors of RAP included creatinine clearance (CrCl) 25-60 mL/min (OR = 3.34; 95% CI: 1.83-9.46), CrCl < 25 mL/min (OR = 4.26; 95% CI: 1.04-17.47), preoperative oxygen saturation ≤ 94% (OR = 16.78; 95% CI 3.99-70.57), and use of aminosteroid muscle relaxants (OR = 3.00; 95% CI: 1.23-7.31). The immediate outcomes of RAP were unplanned ICU admission (65.22%), major respiratory events (19.57%), and cardiovascular events (19.57%).

CONCLUSIONS Independent risk factors of RAP were renal insufficiency, CrCl < 60 mL/min, preoperative oxygen saturation ≤ 94%, creatinine clearance 25-60 mL/min, and use of an aminosteroid muscle relaxant. Proper evaluation and management before extubation could help prevent the occurrence of RAP.

KEYWORDS reintubation, PACU, postoperative outcome, anesthesia

INTRODUCTION

Reintubation after planned extubation (RAP) is defined as intubation that occurs after planned extubation in patients receiving general anesthesia (1). RAP can lead to unplanned intensive care admission, desaturation, hemodynamic instability, and cardiac arrest within 24 hours after reintubation. Additionally, RAP is associ-

ated with prolonged respiratory support (1-5), ventilator-associated pneumonia (6), and prolonged hospital stay (5,7). These, all of which can lead to increased morbidity and mortality (1-3,8).

Previous studies conducted in different hospitals have reported the incidence of RAP in the Postanesthetic Care Unit (PACU) ranging from

0.06% to 0.27% (3,9-12). However, according to the Thai Anesthesia Incidents Study (THAI Study), the first multi-center prospective cohort study comprising 20 hospitals (7 university, 5 tertiary, 4 secondary, and 4 primary care hospitals) across Thailand during 2003-2004, reported that the incidence of RAP was 0.027% (1). Furthermore, a study of the overall incidence of RAP from Perioperative and Anesthetic Adverse Events in Thailand (PAAAd THAI) initiated by the Royal College of Anesthesiologists of Thailand (RCAT) in 2015, conducted in 22 university and non-university hospitals in Thailand was 0.0011% (5).

Independent risk factors associated with RAP can be divided into anesthesia-related, patient-related, and surgery-related factors. According to a previous retrospective cohort study report in Chiang Mai University Hospital, the incidence of RAP was 0.27% (10). In that 2009 study, the independent risk factors statistically significantly related to RAP were age over 50 years, American Society of Anesthesiologists physical status (ASA PS) 3-4, and intraabdominal surgery (10). The anesthetic management staff and other personnel in our institution have changed since that time, so the present study was conducted to explore the current incidence, relevant risk factors, possible causes, and outcomes of RAP.

Objectives

The study aimed to determine the incidence, risk factors, possible causes, and clinical outcomes of RAP in postoperative patients.

METHODS

This retrospective case-control study was conducted at the Department of Anesthesiology, Faculty of Medicine, Chiang Mai University. After obtaining Institutional Research Ethical Committee approval (certificate no.474/2016), adult patients who had received either elective or emergency non-cardiac surgery under general anesthesia between 2013 and 2017 were included. Patient informed consent was waived because of the retrospective nature of the study. The adverse events and causal factors related to RAP were retrieved from the electronic database, which was reviewed and summarized by

the consensus of the Quality Assurance Committee in our department. Two investigators (SK and BS) reviewed the incident cases and discussed possible causes of RAP. If there were disagreements between the reviewers, the third reviewer (TP) would make the final decision. The definition of RAP, according to the THAI study, is a patient who received general anesthesia being intubated again after extubation within 24 hours after anesthesia (1).

Variables and clinical outcomes

Patient characteristics and demographic data (see Supplementary Data) included age, gender, body mass index (BMI), ASA PS, comorbidities, and preoperative laboratory test results.

Data on the site of the operation (thoracic surgery, intracranial surgery, head, eyes, ears, nose and throat surgery (HEENT), airway, intra-abdomen, superficial, extremities, and others), intraoperative data, and anesthetic agents were collected.

The significant events within 24 hours after surgery were recorded as immediate clinical outcomes. Immediate clinical outcomes included unplanned intensive care unit (ICU) admission, major respiratory events, cardiovascular events, and neurological events. In-hospital events that occurred within 7 days after surgery were defined as delayed clinical outcomes, e.g., prolonged ventilator support and mortality.

Patients

Definition of cases

All adult patients documented as RAP in the operating theater or PACU were defined as index cases.

Selection of control

An electronic anesthetic and postanesthetic records database was reviewed to identify the control group. Control cases, patients who were successfully extubated after undergoing general anesthesia on the same operating day and time as the incidence cases, were randomly selected. Due to the low incidence of RAP, we decided to use a ratio of index to control cases of 1:4.

Statistical analysis

Categorical data were reported as frequencies and percentages and were compared between

groups using an exact probability test. Continuous variables were presented as means and standard deviations for normally distributed data or as medians (interquartile range) for non-normal distribution. Data distribution was verified by the Shapiro–Wilk test. Comparative analysis of continuous data between the two groups was conducted using the student's t-test or the Wilcoxon rank-sum test according to the distribution of the data. Univariable logistic regression was used to determine the risk factors of RAP. All univariable risk factors with $p < 0.2$ were selected and included in the multivariable logistic regression. Risk factors are presented as odds ratios (OR) and confidence intervals (CI). $P < 0.05$ were considered statistically significant. STATA 14.0 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

The sample size was calculated based on the OR of potential risk factors for RAP from a previous study (13). A minimum of 25 cases with

RAP and 100 control cases were required with a power of 80% and α error of 5%.

RESULTS

From 2013 to 2017, 32,463 patients required general anesthesia with endotracheal intubation in Maharaj Nakhon Chiang Mai Hospital. Forty-six patients had RAP. The control group included 184 patients who had been successfully extubated who were identified by time-matching selection. The incidence of RAP was 0.14% (46 cases). The mean age of patients with RAP was 60 years, and for non-RAP patients was 51.5 years. Most patients in both groups were male (56.5% in the RAP group and 51.6% in the non-RAP group). (Table 1)

The most common sites of the operations were intra-abdomen (23.9% of the RAP group, 35.8% of the non-RAP group), extremities (23.9% of the RAP group, 23.3% of the non-RAP group), and head and neck surgery (21.7% of the RAP group, 15.8% of the non-RAP group). The number

Table 1. Patient characteristics and demographic data of patients with and without RAP

Variables	RAP (N=46)	Non-RAP (N=184)	p-value
Age(years) median (P25-P75)	60 (38-69)	51.5 (34-65)	0.064
< 70	35 (76.1)	157 (85.3)	
≥ 70	11 (23.9)	27 (14.7)	
Sex (n,%)			0.552
Male	26 (56.5)	95 (51.6)	
Female	20 (43.5)	89 (48.4)	
BMI (kg/m ²)			0.613
Mean±SD	23.2±5.1	23.5±4.6	
ASA PS 1 (n,%)	5 (10.9)	58 (31.5)	< 0.001
ASA PS 2	15 (32.6)	95 (51.6)	
ASA PS 3	26 (56.5)	31 (16.9)	
Comorbidities (n, %)			
Hypertension	21 (45.6)	64 (34.8)	0.172
Diabetes mellitus	11 (23.9)	20 (10.9)	0.021
Respiratory disease	11 (23.9)	12 (6.5)	< 0.001
Coronary artery disease	3 (6.5)	11 (6.0)	0.89
Renal insufficiency	23 (50.0)	25 (13.6)	< 0.001
History of smoking	24 (52.2)	60 (42.6)	0.014
Laboratory (mean±SD)			
Hb (g/dL)	11.8±2.1	12.1±2.1	0.399
K (mmol/L)	4.2±0.8	4.0±0.5	0.007
Creatinine clearance	57.2 (25.3-81.8)	84.4 (63.9-110.7)	< 0.001
Median (P25-P75)			
> 60	22 (47.8)	143 (77.7)	
25-60	14 (30.4)	30 (16.3)	
< 25	10 (21.8)	11 (6.0)	

RAP, reintubation after planned extubation; BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; Hb, hemoglobin

Table 2. Intraoperative and anesthetic details between patients with and without RAP

Variables	RAP (N=46)	Non-RAP (N=184)	p-value
Site of operation (n, %)			
Thoracic	4 (8.7)	7 (3.8)	0.082
Intra-cranial	3 (6.5)	2 (1.1)	
HEENT	10 (21.7)	29 (15.8)	
Airway	0	11 (6.0)	
Intra-abdomen	11 (23.9)	66 (35.8)	
Superficial	6 (13.0)	16 (8.7)	
Extremities	11 (23.9)	41 (23.3)	
Others	1 (2.2)	12 (6.5)	
Type of procedure (n,%)			0.015
Elective surgery	23 (50.0)	127 (69.0)	
Emergency surgery	23 (50.0)	57 (31.0)	
Induction agents (n,%)			0.072
Thiopental	13 (28.3)	37 (20.1)	
Propofol	28 (60.9)	137 (74.5)	
Etomidate	4 (8.7)	9 (4.9)	
Inhalation	1 (2.1)	1 (0.5)	
Neuromuscular blocking agents (n, %)			0.009
Aminosteroid compound	9 (20.0)	11 (5.9)	
Rocuronium	9 (20.0)	6 (3.2)	
Pancuronium	0	5 (2.7)	
Benzylisoquinolinium compound	36 (78.2)	168 (91.3)	
Atracurium	20 (43.4)	104 (56.5)	
Cisatracurium	16 (34.8)	67 (36.4)	
Succinylcholine	0	3 (1.6)	
Reverse neuromuscular blocking agents (n, %)			
Yes	46 (100)	184 (100)	
Operation time (min)			0.439
Median (P25-P75)	120 (85-200)	140 (90-210)	
Intraoperative blood loss (ml)			0.911
Median (P25-P75)	50 (20-200)	50 (10-200)	
Intraoperative crystalloid administration (mL)	400 (280-1,000)	450 (250-875)	0.790
Median (P25-P75)			
Intubating performers (n,%)			< 0.001
Anesthesiologists	4 (8.7)	1 (0.54)	
3 rd year resident	17 (36.9)	45 (24.6)	
2 nd year resident	25 (54.4)	137 (74.5)	

HEENT, (head, eyes, ears, nose, and throat surgery)

of patients with ASA PS 3 in the RAP group (56.5%) was significantly higher than in the non-RAP group (16.9%). (Table 2)

Univariable logistic regression showed age equal to or higher than 70 years, hypertension, diabetes mellitus, current smokers, emergency surgery, creatinine clearance (CrCl), preoperative room air oxygen saturation (SaO₂) less than 94%, and aminosteroid compound administration to be potential risk factors.

After multivariable-adjusted analysis, the independent risk factors of RAP included CrCl 25-60 mL/min (OR = 3.34; 95% (CI): 1.83-9.46), CrCl < 25 mL/min (OR = 4.26; 95% CI: 1.04-17.47), preoperative room air SaO₂ ≤ 94% (OR

= 16.78; 95% CI 3.99-70.57) and use of an aminosteroid muscle relaxant (OR = 3.00; 95% CI: 1.23-7.31). (Table 3)

Possible causes of RAP are presented in Table S1. In fourteen patients (30.4%) who had low-minute ventilation, hypoventilation was suspected of being a cause of RAP (14). In addition, 13% of the patients were re-intubated due to hemodynamic instability and upper airway obstruction. Other possible causes of RAP were mental status change, volume overload, respiratory failure, acute bronchospasm, and surgical bleeding.

The immediate outcomes of RAP were unplanned ICU admission (65.22%), major res-

Table 3. Univariable and multivariable logistic regression of RAP

Variables	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age ≥ 70 years	1.83 (0.83-4.03)	0.135	0.54 (0.16-1.88)	0.338
Male	0.82 (0.43-1.57)	0.553		
Hypertension	1.50 (0.78-2.89)	0.223		
Diabetes Mellitus	2.44 (1.08-5.52)	0.032	1.26 (0.41-3.88)	0.691
Chronic liver disease	0.79 (0.17-3.74)	0.767		
Current smokers	2.25 (1.17-4.34)	0.015	1.67 (0.66-3.30)	0.340
Emergency surgery	2.12 (1.10-4.08)	0.025	1.05 (0.47-2.34)	0.897
Intrathoracic/abdominal surgery	0.74 (0.37-1.46)	0.379		
Cr clearance > 60	1	Reference	1	Reference
Cr clearance 25-60	2.80 (1.29-6.07)		3.34 (1.83-9.46)	0.023
Cr clearance < 25	5.83 (2.21-15.32)		4.26 (1.04-17.47)	0.044
Preoperative oxygen saturation (≤ 94%)	18.96 (5.03-71.47)	< 0.001	16.78 (3.99-70.57)	<0.001
Aminosteroid compound administration	3.59 (1.46-8.82)	0.005	3.00 (1.23-7.31)	0.016

Cr (Creatinine) OR (Odds ratio)

piratory events (19.57%), and cardiovascular events (19.57%). (Table 4)

Seventy-two percent of patients in the RAP group were successfully extubated. Most (34.78%) were extubated within 24 hours in PACU and ICU. In addition, five patients in the RAP group needed mechanical ventilation after surgery for more than 48 hours. Two patients in the RAP group died within 24 hours of ICU admission. Twenty-five patients in the RAP group (54.35%) required mechanical ventilatory support for more than 24 hours. (Table S2)

In the RAP group, the patients were re-intubated within 30 minutes (47.83%), between 30 and 60 minutes (30.43%), and more than 60 minutes (21.74%) after extubation. RAP occurred frequently in the PACU (58.70%), operating room (36.96%), and ICU (4.35%). (Table S3)

DISCUSSION

The incidence of RAP in this study was 0.14%. The independent risk factors of RAP included CrCl < 60 mL/min, preoperative room air SaO₂ ≤ 94%, and use of aminosteroid muscle relaxants. In addition, we found that patients in the RAP group had unplanned ICU admission, major respiratory events major cardiovascular events, and mechanical ventilatory support for more than 24 hours, statistically significantly higher than the incidence in the control group, 65.22%, 19.57%, 19.57%, and 54.35%, respectively.

The incidence of RAP in this study was lower than in a study by Bunchungmongkol et al.

Table 4. Immediate and delayed clinical outcomes after RAP

Clinical outcomes	N (%)
Immediate clinical outcomes	
Unplanned ICU admission	30
Major respiratory events	(65.22)
Pulmonary edema	9 (19.57)
Acute respiratory distress syndrome	8 (17.39)
Pulmonary embolism	1 (2.17)
Major cardiovascular events	1 (2.17)
Arrhythmia (atrial fibrillation)	9 (19.57)
Acute congestive heart failure	5 (10.87)
Acute myocardial ischemia	3 (6.52)
Major neurological events	1 (2.17)
Hemiparesis	4 (8.70)
Seizure	3 (6.52)
Delayed clinical outcomes	
Prolonged ventilator support	1 (2.17)
1-3 days	20 (43.48)
> 3 days	5 (10.87)
Death	2 (4.35)

which was conducted between 2004-2006 in our institution which reported the incidence of RAP to be 0.0027% (10). The incidence of RAP in our study was also lower than the results in a study in another institution in Thailand (12). The incidence of RAP events in that study was estimated to be 0.0017% (12). The lower incidence of RAP in our study was probably due to the use newer developed and shorter-acting anesthetic agents, including propofol and desflurane (15, 16), as well as more advanced brain function monitoring, including bispectral index (BIS), which can help anesthesiologists adjust the depth of anesthesia and improve the

recovery time.

Previous studies have reported various risk factors related to RAP (Table S2). Anesthetic-related factors identified include inappropriate fluid management (10), residual neuromuscular blockade (1,3,9,10,12), sedative effect (1,9,12), inadequate airway care (1,9,12,17), and inexperienced anesthesia personnel (5,10,18). Extreme age (age < 1 and > 70 years) (3,11,19), chronic pulmonary disease (3), preoperative hypoalbuminemia (3), renal insufficiency (3), and ASA PS status > 3 (3,10,11) were patient-related factors. Surgery-related factors were emergency surgery (3), head and neck surgery (3,11), cardiothoracic surgery (3), airway surgery (3,18,20), and operative time of more than three hours (3).

In our study, renal impairment (CrCl 25–60 mL/min, < 25 mL/min) and use of an aminosteroid neuromuscular blocking agent were the risk factors of RAP, which is in concordance with Rujirojindakul et al. (3) and Lin, H-T et al. (18).

Preoperative room air SaO₂ of less than 94%, a condition commonly found in patients with preexisting chronic lung disease, was found to be related to RAP.

In previous studies, low SaO₂ was also reported to be one of the most common risk factors of postoperative mechanical ventilatory support longer than 24 hours (21,22).

The RAP events mainly occurred within 30 minutes after extubation. These findings may be indicative of inappropriate evaluation of the patients before considering extubation. To reduce the risk of inappropriate evaluation, extubation criteria should be revised and their importance reinforced to all levels of resident anesthesiologists and anesthesia personnel during quality assurance activities in the department. Patients who are at risk of RAP should be extubated under the supervision of senior anesthesiologists.

Hypoventilation has been found to be one of the most common causes of RAP. Hypoventilation and desaturation in the PACU can be caused by the residual effects of neuromuscular blocking and sedative medications (23). Previous studies have reported that residual neuromuscular blockade increased the risk of RAP in PACU in cases with pulmonary com-

plications (24,25). The use of intraoperative neuromuscular monitoring could reduce the risk of residual neuromuscular blockade (26). In addition, some newer reversal agents, including sugammadex, a direct reversal agent of rocuronium and vecuronium, have been associated with a lower incidence of postoperative reintubation (20) and a lower risk of residual neuromuscular blocking effect compared to neostigmine (20,24). Despite its advantages, sugammadex was not widely administered as a routine practice during 2013–2017 due to its higher cost compared with neostigmine. All patients in this study received neostigmine as a reversal agent. Moreover, neuromuscular monitoring was used only in selected cases due to the limited availability of this equipment in our department.

Proposed recommendations to minimize the risk of RAP include the following. First, the use of perioperative neuromuscular monitoring and sugammadex should be specified, particularly in patients at risk of RAP. Second, if a tracheal extubation is to be performed by an inexperienced anesthesia resident, it should be performed under the supervision of senior anesthesiologists or staff members. Finally, delayed extubation and mechanical ventilatory support should be considered especially for high-risk RAP patients.

Strengths

The study's strengths include identifying potential risk factors, possible causes, and postoperative clinical outcomes of RAP which can be applied in daily anesthesia practice to increase awareness of the risk of RAP and which can help ensure in satisfactory extubation.

Limitations

The study design is retrospective, so it is impossible to determine all patient variables and outcomes. Therefore, some potential risk factors of RAP that could influence clinical judgments might not have been identified. Additionally, as this was a single-center study, the results might not be generalizable to other institutions with different populations and clinical practices. Although we tried to recruit all cases of RAP, the sample size was small.

Further study with a larger sample size is needed to increase the accuracy of information regarding the relevant risk factors of RAP.

CONCLUSIONS

RAP is one of the critical adverse events which can occur after anesthesia. RAP increases the rate of unplanned ICU admissions and prolongs mechanical ventilatory support. Independent risk factors of RAP include creatinine clearance < 60 mL/min, preoperative oxygen saturation \leq 94%, and use of an aminosteroid muscle relaxant. The practice of perioperative neuromuscular monitoring, the strict observance of extubation criteria and conducting extubation under the supervision of staff consultants should be encouraged, especially in the case of high-risk patients with RAP.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the publication of this paper.

ADDITIONAL INFORMATION

Data availability

The data used in this study are not publicly available due to participant privacy, but are available from the corresponding author upon reasonable request.

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Supplementary data

Definitions of variables and clinical outcomes

Patients' characteristics and demographic data

The present of comorbidities were defined from the patients' preoperative evaluation and medical records.

- a. Respiratory disease was defined as chronic obstructive pulmonary disease (COPD), asthma, or interstitial lung disease.
- b. Coronary artery disease was defined as the patients who had history of coronary artery disease before surgery.
- c. Renal insufficiency was defined as creatinine clearance < 60 ml/min.

Immediate clinical outcomes: The significant events within 24 hours after surgery

1. Unplanned intensive care unit (ICU) admission was defined as the patients were unexpectedly admitted in the ICU after surgery.
2. Major respiratory events were included pulmonary edema, acute respiratory distress syndrome and pulmonary embolism.
3. Major cardiovascular events were included arrhythmia, acute congestive heart failure and acute myocardial ischemia.
4. Major neurological events were included hemiparesis, seizure and stroke.

Delayed clinical outcomes: in-hospital events occurred within 7 days after surgery.

1. Prolonged ventilator support was defined as the patients needed mechanical ventilatory support for more than 48 hours.
2. In-hospital mortality was included all-cause of death during admission within 7 days after surgery

Supplementary tables**Table S1 Causes of RAP**

Causes	Number (%)
Hypoventilation	14 (30.4)
Hemodynamic instability	6 (13.0)
Mental status change	4 (8.7)
Acute bronchospasm	5 (10.9)
Upper airway obstruction	6 (13.0)
Surgical bleeding	3 (6.5)
Volume overload	4 (8.7)
Respiratory failure	4 (8.7)

Table S2 Factors Related to RAP

Factor-related	Number (%)
Patient factors	32 (69.6)
- Respiratory disease	11 (34.4)
- Sepsis	6 (18.7)
- Volume overload	6 (18.7)
- Cardiovascular disease	6 (18.7)
- Neurological disease	3 (9.4)
Anesthetic factors	25 (54.3)
- Oversedation	14 (56.0)
- Residual neuromuscular blockade	7 (28.0)
- Inappropriate fluid management	4 (16.0)
Surgical factors	7 (15.2)
- Surgical complication	4 (57.1)
- Bleeding	3 (42.9)

Table S3 Time to Reintubation and Successful Extubation after RAP

Time to reintubation	Number (%)
Time to reintubation (min) Median (P25-P75)	30 (5-60)
<30 min	22 (47.8)
30-60 min	14 (30.4)
>60 min	10 (21.7)
Place of RAP	
Operating room	17 (37.0)
PACU	27 (58.7)
ICU	2 (4.3)
Successful extubation after RAP	
Recovery room	7 (15.2)
Within 6 hr	4 (8.7)
Within 24 hr	16 (34.8)
2-3 days	14 (30.4)
> 3 days	5 (10.9)

Factors Related to Healthcare Utilization of Physical Discomfort in Electronic Device Users at Home

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ABSTRACT

OBJECTIVE This study aims to discern the factors influencing the utilization of healthcare services among individuals experiencing physical discomfort from electronic device usage at home.

METHODS A retrospective cross-sectional study was performed. The sociodemographic information, exercise habits, working organization, behavioral patterns, treatment methods, healthcare service usage, and responses to the modified online Thai Cornell Musculoskeletal Discomfort Questionnaires (CMDQ) were reviewed from the web-based online questionnaire surveyed from November 29th to December 28th, 2021. The impact of various factors on healthcare utilization was assessed using multivariable logistic regression.

RESULTS Three hundred and thirty-four participants were included, primarily female (70%) and with a mean age of 35.0±7.3 years. Most common was neck discomfort (24.9%) with 48.5% experiencing chronic symptoms and 52.1% reporting severe discomfort. The majority (72.4%) indicated discomfort in multiple areas (5-7 regions). The methods of treatment consisted of complementary and alternative medicine (23.7%), conventional medicine (16.5%), and both (22.5%). Healthcare services were accessed by 56% of the participants, with 35.9% choosing private healthcare. Healthcare utilization was significantly associated with being aged ≥ 45 years (odd ratio = 5.476, 95%CI 1.953, 15.356), short break durations (odd ratio = 1.809, 95%CI 1.010, 3.240), having an ergonomic policy in the organization (odd ratio = 2.119, 95%CI 1.161, 3.866), chronic symptoms (odd ratio = 1.901, 95%CI 1.047, 3.452), severe discomfort (odd ratio = 2.121, 95%CI 1.218, 3.693), and multiple discomfort areas (odd ratio = 2.384, 95%CI 1.060, 5.362).

CONCLUSIONS Healthcare utilization for addressing physical discomfort among electronic device users is influenced by various factors, including age, short break duration, ergonomic policy in the organization, chronic or severe discomfort, and the extent of discomfort distribution. Prioritizing healthcare facilities for individuals experiencing chronic and severe discomfort is warranted.

KEYWORDS musculoskeletal pain, consumer health information, health-seeking behavior, computers, sitting position

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INTRODUCTION

Pain is one of the leading causes of physical discomfort and is characterized by an unpleasant feeling (1). Almost 69.7% of office workers reported experiencing musculoskeletal discomfort (2). Neck, shoulder, and back pain were the most frequent complaints. Intense pain affected 30% of those people. The risks were obesity, high stress, inappropriate seating (3), and longer working duration (4). With the development of technology, people have more opportunities to work from home, particularly during the Coronavirus 2019 outbreak. A recent study found the prevalence of physical discomfort increased to 97% during the pandemic. The majority of them suffered from chronic and severe pain (3). However, the prior study concentrated on risk factors for musculoskeletal disorders in office employees, with no investigation on healthcare utilization.

Previous research showed that the prevalence of healthcare seeking behavior for musculoskeletal pain differs globally, ranging between 20% and 60% (5-7). Predisposing factors (e.g. demographic, social, and mental factors), enabling factors (e.g. income, health insurance), and need factors (a person's health status or severity) are the aspects of understanding patient usage of healthcare. These factors all contribute to the utilization of healthcare resources (8). Prior studies revealed the significant predictors of increased healthcare access in musculoskeletal conditions were of an older age, multiple pain areas (9), disability, and the occurrence of an adverse medication reaction (5). According to research on chronic musculoskeletal pain by Sugai and colleagues, choosing physician consultation in the hospital or clinic was linked with female, high income, suffering from moderate to severe pain, and high pain intensity (6). Moreover, a variety of healthcare facilities, such as clinics and primary care, may have an effect on the sort of therapy chosen. One study found that persistent musculoskeletal pain was mostly managed in primary care rather than secondary care (10). Due to differences in population, diagnosis, and the healthcare system, each study was varied.

To determine the scope of the issue of muscu-

loskeletal discomfort, especially in developing nations, epidemiological data is crucial. This data can be utilized to support and plan strategies for the healthcare setting. Thailand still lacks data on this population. The present study aims to identify factors associated with receiving healthcare services in electronic device users who worked from home and were experiencing physical discomfort.

METHODS

Study design

This study was a retrospective cross-sectional study. It was approved by the Ethics Committee, Lerdsin Hospital, and has been performed in accordance with the ethics standards of the Declaration of Helsinki. The certification number is LH661006. We reviewed the data from the questionnaire that was surveyed from 29th November to 28th December 2021 by Google Forms as the platform for a web-based survey. The survey was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University 620/2564 (IRB3), certification number 828/2021. Most of the extracted data has not been published before. However, the overlapping contents included mean age, gender, group of stress level, electronic devices used, symptoms duration, and group of discomfort severity were similar to the previous publication (3).

Participants

The inclusion criteria were participants aged between 18-60 years old who spent more than 50% of the electronic device usage time in a sitting position at home. They had to use the device for more than 2 hours per day, at least 3 days per week for at least 2 months. They had physical discomfort in at least one upper-body area. The exclusion criteria included individuals with a history of musculoskeletal or neurological conditions or surgery that resulted in abnormal sensation or discomfort in a sitting position, and participants who had incomplete data. A total of 365 participants data was reviewed. Of that total, 31 participants met the exclusion criteria (Figure 1). The eligible data had 334 participants.

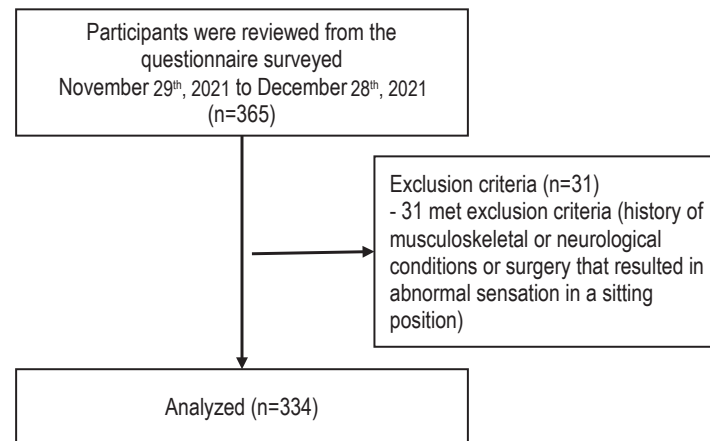


Figure 1. Flow chart of participants recruitment

Data sources

Operation definition

Healthcare utilization was defined as the use of healthcare services including government/private hospital or clinic.

Self-care was defined as any means of individuals to manage physical discomfort without healthcare service including self-modality, ergonomic adjustment, muscle stretching, exercise, and yoga.

Conventional medicine was defined as treatments that is widely accepted and used by most healthcare professionals including medication and/or physical therapy.

Complementary and alternative medicine (CAM) was defined as any means of treatments that falls outside of conventional medicine including massage, acupuncture, and chiropractic.

Sociodemographic data

The data consisted of gender, age, marital status, education level, income, stress levels in the past few weeks on a 5-point Likert scale (0=none, 4=very stressful), physical exercise, sleep duration, types and ergonomic policies of the organization the participants were working with, working behaviors, healthcare rights, methods of treatment (conventional medicine, CAM), self-care, healthcare service (government or private), frequency of healthcare access, and symptoms duration.

Physical discomfort data

Modified online Thai-translated Cornell Musculoskeletal Discomfort Questionnaires (CMDQ) was used to assess physical discomfort. This modified version selected areas of interest to be neck, left and right shoulders, left and

right upper back, and left and right lower back. With regard to Discomfort, Frequency, and Interference Scores, we used only the Discomfort Score because from the previous study, all these three scores were strongly related to each other (3). The Discomfort score was divided into three categories: slightly, moderately, and very uncomfortable. We classified the severity of discomfort into two groups: non-severe and severe (participants answered very uncomfortable in at least one area). The number of discomfort areas was divided into three groups: less than 3 areas defined as few discomfort areas group, 3-4 areas was several discomfort areas group, and 5-7 areas was multiple discomfort areas group.

Study size estimation

The sample size was calculated by using The Rule of Thumb. One factor used 5-10 samples. We estimated approximately 15 factors affected healthcare utilization. There were two behaviors (use and not use healthcare service). The calculated sample size was 300 samples in total. Eventually, we used all 334 samples.

Statistical analysis

Data were analyzed using the PASW Statistics version 18.0 program (SPSS Inc., Chicago, IL., USA). A p -value of 0.05 or less was accepted as statistical significance. Quantitative data were reported as numbers and percentages. Means and standard deviations were used as summary measures for normally distributed data. Pearson's chi-squared test was performed to analyze the differences in categorical data (factors and

types of healthcare utilization). Multivariable logistic regression analysis was used to find associations between possible factors (socio-demographic data, stress level, sleep duration, working behaviors, symptoms duration, discomfort severity, and number of discomfort area) and receiving healthcare service. Confidence Interval for each diagnostic parameter was also estimated at 95% level.

RESULTS

There were 334 participants who met the criteria. According to the baseline characteristics, most of the participants were female (70%). The mean age was 35.0 ± 7.3 years and 68.3% were single. Most of the education level was Bachelor's degree or higher (97.6%). Most of the participants had enough income compared to expenses (45.8%). High stress level was found in 41.3% of the participants. The majority of participants (47.3%) reported exercising for at least 15 minutes per session 1-2 times per week. Most of them slept for ≥ 6 hours per night (72.2%). Laptop computers were commonly used (66.2%) (Table 1).

Participants who worked in private organizations made up 51.5% of the total, with 33.2% working for government institutions. They worked for ≥ 6 hours without a break (62.3%). Less than 30 minutes of break duration was reported by 56.9% of the participants. Around half of the participants (51.8%) stated that there was no ergonomic policy in their organizations (Table 1).

The most common severe discomfort area was neck (24.9%), followed by right shoulder (23.1%). Chronic symptoms and severe discomfort were reported at 48.5% and 52.1% respectively. Multiple discomfort areas group was the highest (72.4%). Almost 96% of participants did not do self-care. The methods of treatment showed conventional medicine (16.5%), CAM (23.7%), or both (22.5%). More than half of the participants (56%) received healthcare services, among those, private healthcare was chosen by 35.9%. Most participants visited the hospital when they occasionally got symptoms (79.6%) (Table 1). Each participant had at least one healthcare rights. Social Security Scheme (50%), Health Insurance (35.6%), and Civil

Table 1. Demographic data of participants

Demographic data	N (%)
Gender	
Female	235 (70.4)
Male	99 (29.4)
Age (year)	35.0 (7.3) ^t
< 45	304 (91.0)
≥ 45	30 (9.0)
Marital status	
Single	228 (68.3)
Married	101 (30.2)
Widowed/divorced	5 (1.5)
Education	
Lower Bachelor's degree	8 (2.4)
Bachelor's degree	147 (44.0)
Upper Bachelor's degree	179 (53.6)
Income	
Less than expenses	44 (13.2)
Equal expenses	137 (41.0)
More than expenses	153 (45.8)
Stress level (Likert)	
0-2	196 (58.7)
3-4	138 (41.3)
Physical exercise	
No	75 (22.5)
1-2 times per week	158 (47.3)
≥ 3 times per week	101 (30.2)
Sleep duration	
< 6 hours	93 (27.8)
≥ 6 hours	241 (72.2)
Electronic devices used	
Laptop computer	221 (66.2)
Desktop computer	74 (22.1)
Mobile phone	29 (8.7)
Tablet	10 (3.0)
Types of organization	
Government	111 (33.2)
State enterprise	15 (4.5)
Private employee	172 (51.5)
Freelance	36 (10.8)
Working duration without break	
2-4 hours	43 (12.9)
> 4-6 hours	83 (24.9)
> 6 hours	208 (62.3)
Break duration	
< 30 minutes	190 (56.9)
≥ 30 minutes	144 (43.1)
Ergonomic policy	
None	173 (51.8)
Knowledge/workshop	88 (26.3)
Equipment/budget	34 (10.2)
Both knowledge/workshop and equipment/budget	39 (11.7)
Symptoms duration	
< 6 weeks	123 (36.8)
6-12 weeks	49 (14.7)
> 12 weeks	162 (48.5)

Table 1. Demographic data of participants (continue)

Demographic data	N (%)
Areas of severe physical discomfort	n=334
Neck	83 (24.9)
Left shoulder	59 (17.7)
Right shoulder	77 (23.1)
Left upper back	41 (12.3)
Right upper back	57 (17.1)
Left lower back	55 (16.5)
Right lower back	68 (20.4)
Discomfort severity	
Non-severe	160 (47.9)
Severe	174 (52.1)
Number of discomfort area	
Few areas	41 (12.3)
Several areas	51 (15.3)
Multiple areas	242 (72.4)
Self-care	
No	320 (95.8)
Yes	14 (4.2)
Methods of treatment	
None	125 (37.3)
Conventional medicine	55 (16.5)
CAM	79 (23.7)
Conventional medicine and CAM	75 (22.5)
Healthcare service	
None	147 (44.0)
Government	26 (7.8)
Private	120 (35.9)
Both	41 (12.3)
Frequency of receiving healthcare	n=187
Weekly	26 (13.9)
Monthly	12 (6.4)
Occasionally	149 (79.6)

^aMean (SD), CAM; complementary and alternative medicine

Servant Medical Benefit Scheme (22.5%) were the most common.

The factors that impacted healthcare utilization were aged ≥ 45 years (odd ratio = 5.476, 95%CI 1.953, 15.356), break duration < 30 minutes (odd ratio = 1.809, 95%CI 1.010, 3.240) having an ergonomic policy in the organization (odd ratio = 2.119, 95%CI 1.161, 3.866), chronic symptoms (odd ratio = 1.901, 95%CI 1.047, 3.452), severe discomfort (odd ratio = 2.121, 95%CI 1.218, 3.693) and multiple discomfort areas group (odd ratio = 2.384, 95%CI 1.060, 5.362) (Table 2).

They more frequently sought out private healthcare service than either government healthcare or both in the age of under 45 ($p = 0.010$), break duration < 30 minutes ($p = 0.039$), chronic symptoms ($p < 0.001$), severe discomfort

($p < 0.001$), and multiple discomfort areas group ($p < 0.001$) (Table 3).

DISCUSSION

The present study is the first to demonstrate an association between physical discomfort and seeking healthcare utilization in electronic device users who worked from home in sitting position. Even though the population and diagnosis of musculoskeletal pain were heterogeneous in several studies, the characteristics relating to the stage and severity of the disease were crucial considerations, whereas demographic status had little impact on the decision to seek healthcare (11). The major findings in our study were more pronounced in the domain of short break duration, persistent, severe, and widespread discomfort.

Around half of the participants (56%) received healthcare services. This ratio was comparable to Sugai's finding. We discovered no association between cost and receiving healthcare services, contrary to what Sugai indicated (6). This could be because the majority of participants in this study had greater income than expenses (45.8%), and most basic musculoskeletal condition treatments in Thailand are reimbursable. The age ≥ 45 years (9.0%) and chronic symptoms (48.5%) were related to receiving healthcare services. Growing older is typically accompanied by complex health issues and is frequently linked with chronic musculoskeletal pain (12). Older age may exacerbate the underlying disorders and make people concerned about serious illnesses. Therefore, they sought to consult a doctor for a precise diagnosis and more competence (6).

Severe discomfort (52.1%) and multiple discomfort areas (72.4%), similar to the other studies, were additional characteristics associated with receiving healthcare services. The studies also reported that the greater the number of pain areas related to the greater the amount of healthcare contact in the long-run (9) and the decline in physical and mental quality of life (QoL) (13, 14). However, high stress levels were not connected with seeking healthcare service in this study. In spite of the fact that high stress levels were related to severe discomfort in computer users (3), they

Table 2. Univariate and multivariate analysis to identify factors independently associated with seeking healthcare service

Factors	Healthcare service			
	Univariable analysis ¹		Multivariable analysis ²	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Gender				
Female	Ref.	0.890	Ref.	0.949
Male	1.034 (0.644, 1.660)		0.982 (0.567, 1.702)	
Age (years)				
< 45	Ref.	0.005	Ref.	0.001*
≥ 45	3.460 (1.375, 8.705)		5.476 (1.953, 15.356)	
Stress level				
0-2	Ref.	0.289	Ref.	0.952
3-4	1.269 (0.817, 1.972)		0.984 (0.575, 1.683)	
Income				
Less expenses	Ref.	0.253	Ref.	0.185
Equal expenses	1.495 (0.756, 2.958)		1.674 (0.775, 3.617)	
More expenses	1.761 (0.896, 3.461)		2.049 (0.952, 4.414)	
Physical exercise				
≥ 3 times per week	Ref.	0.391	Ref.	0.535
1-2 times per week	1.359 (0.783, 2.359)		1.228 (0.642, 2.350)	
No	1.503 (0.823, 2.745)		1.506 (0.734, 3.088)	
Sleep duration				
≥ 6 hours	Ref.	0.318	Ref.	0.089
< 6 hours	1.278 (0.790, 2.065)		1.572 (0.933, 2.649)	
Working duration				
2-4 hours	Ref.	0.612	Ref.	0.110
> 4-6 hours	0.820 (0.492, 1.366)		0.612 (0.334, 1.122)	
> 6 hours	1.167 (0.597, 2.280)		1.947 (0.861, 4.404)	
Break duration				
≥ 30 minutes	Ref.	0.033	Ref.	0.046*
< 30 minutes	1.612 (1.040, 2.497)		1.809 (1.010, 3.240)	
Ergonomic policy				
None	Ref.	0.075	Ref.	0.014*
Knowledge/workshop	1.614 (0.953, 2.733)		2.119 (1.161, 3.866)	
Equipment/budget	1.168 (0.557, 2.448)		1.360 (0.586, 3.158)	
Both	1.193 (0.593, 2.403)		1.346 (0.630, 2.878)	
Symptoms duration				
< 6 weeks	Ref.	< 0.001	Ref.	0.035*
6-12 weeks	1.292 (0.663, 2.515)		0.768 (0.365, 1.619)	
> 12 weeks	3.467 (2.118, 5.678)		1.901 (1.047, 3.452)	
Discomfort severity				
Non-severe	Ref.	< 0.001	Ref.	0.008*
Severe	3.085 (1.968, 4.834)		2.121 (1.218, 3.693)	
Number of discomfort area				
Few areas	Ref.	< 0.001	Ref.	0.036*
Several areas	1.279 (0.536, 3.049)		1.227 (0.311, 2.202)	
Multiple areas	3.837 (1.890, 7.791)		2.384 (1.060, 5.362)	
Self-care				0.098
No	Ref.	0.008	Ref.	
Yes	0.202 (0.055, 0.736)		0.278 (0.064, 1.202)	

¹Chi-square test, ²Multiple logistic regression.

*Statistically significant, CI, confidence interval; Ref, reference

Table 3. Characteristic and types of healthcare service comparing in various groups

Variables	Types of healthcare service ¹				p-value
	None (n=147)	Government (n=26)	Private (n=120)	Both (n=41)	
Gender					
Female	104 (70.7%)	19 (73.1%)	85 (70.8%)	27 (65.9%)	0.916
Male	43 (29.3%)	7 (26.9%)	35 (29.2%)	14 (34.1%)	
Age (years)					
< 45	141 (95.9%)	22 (84.6%)	108 (90.0%)	33 (80.5%)	0.010*
≥ 45	6 (4.1%)	4 (15.4%)	12 (10.0%)	8 (19.5%)	
Stress level					
0-2	91 (61.9%)	19 (73.1%)	64 (53.3%)	22 (53.7%)	0.196
3-4	56 (38.1%)	7 (26.9%)	56 (46.7%)	19 (46.3%)	
Income					
Less expenses	24 (16.3%)	3 (11.5%)	14 (11.7%)	3 (7.3%)	0.275
Equal expenses	61 (41.5%)	15 (57.7%)	45 (37.5%)	16 (39.0%)	
More expenses	62 (42.2%)	8 (30.8%)	61 (50.8%)	22 (53.7%)	
Physical exercise					
No	38 (25.9%)	4 (15.4%)	23 (19.2%)	10 (24.4%)	0.808
1-2 times per week	68 (46.2%)	13 (50.0%)	57 (47.5%)	20 (48.8%)	
≥ 3 times per week	41 (27.9%)	9 (34.6%)	40 (33.3%)	11 (26.8%)	
Sleep duration					
< 6 hours	45 (30.6%)	7 (26.9%)	30 (25.0%)	11 (26.8%)	0.790
≥ 6 hours	102 (69.4%)	19 (73.1%)	90 (75.0%)	30 (73.2%)	
Working duration					
2-4 hours	17 (11.6%)	8 (30.8%)	13 (10.8%)	5 (12.2%)	0.062
> 4-6 hours	40 (27.2%)	7 (26.9%)	23 (19.2%)	13 (31.7%)	
> 6 hours	90 (61.2%)	11 (42.3%)	84 (70.0%)	23 (56.1%)	
Break duration					
< 30 minutes	74 (50.3%)	17 (65.4%)	79 (65.8%)	20 (48.8%)	0.039*
≥ 30 minutes	73 (49.7%)	9 (34.6%)	41 (34.2%)	21 (51.5%)	
Ergonomic policy					
None	83 (56.5%)	11 (42.3%)	59 (49.2%)	20 (48.8%)	0.350
Knowledge/workshop	32 (21.8%)	8 (30.8%)	34 (28.3%)	14 (34.1%)	
Equipment/budget	15 (10.2%)	5 (19.2%)	9 (7.5%)	5 (12.2%)	
Both	17 (11.5%)	2 (7.7%)	18 (15.0%)	2 (4.9%)	
Symptoms duration					
< 6 weeks	73 (49.7%)	10 (38.5%)	33 (27.5%)	7 (17.1%)	< 0.001*
6-12 weeks	26 (17.7%)	3 (11.5%)	17 (14.2%)	3 (7.3%)	
> 12 weeks	48 (32.6%)	13 (50.0%)	70 (58.3%)	31 (75.6%)	
Discomfort severity					
Non-severe	93 (63.3%)	13 (50.0%)	42 (35.0%)	12 (29.3%)	< 0.001*
Severe	54 (36.7%)	13 (50.0%)	78 (65.0%)	29 (70.7%)	
Number of discomfort area					
Few areas	28 (19.0%)	1 (3.9%)	11 (9.2%)	1 (2.5%)	< 0.001*
Several areas	32 (21.8%)	3 (11.5%)	10 (8.3%)	6 (14.6%)	
Multiple areas	87 (59.2%)	22 (84.6%)	99 (82.5%)	34 (82.9%)	
Self-care					0.053
No	136 (92.5%)	25 (96.2%)	118 (98.3%)	41 (100.0%)	
Yes	11 (7.5%)	1 (3.8%)	2 (1.7%)	0 (0.0%)	

* Statistically significant, ¹Pearson Chi-square test

might be able to manage it themselves. Alternatively, their discomfort might not have an impact on their overall QoL.

Surprisingly, having an organization's ergonomic policy (knowledge or workshops) was connected with an increase number of subjects receiving healthcare services. This factor

was also not related to severe discomfort or a higher number of discomfort areas. It might be that this policy was ineffectual. Wisit and colleagues revealed that only knowledge was not enough to reduce musculoskeletal discomfort, adjustments in ergonomic behavior and regular practice could do more benefit (15).

Our study found that break duration of < 30 minutes correlated with receiving healthcare services. Long periods of sitting could lead to musculoskeletal pain due to muscle fatigue or overactivity. Changes in behavior in break time promoted improvement of physical discomfort in office workers. Several studies indicated that taking a 15-60 minutes break could help prevent musculoskeletal discomfort in computer users (16, 17). When the discomfort subsides, the need for healthcare may reduce. It should be encouraged to have breaks during work shifts.

There was no significant relationship between physical exercise and the use of healthcare services. One systematic review study indicated that many kinds of exercise for at least 15 minutes three times per week could reduce musculoskeletal discomfort among office workers (18). This study found that 30% of the participants exercised at least 15 minutes three times a week. It seemed to be beneficial in terms of pain. However, there was no significant related between exercise and severe discomfort in subgroup analysis. Thus, severe discomfort might be a key factor to seeking healthcare services in the present study.

Among subjects who underwent healthcare services, considering the healthcare subtype, participants with chronic, severe, and widely spread discomfort appeared to prefer private healthcare over government healthcare in our study. This might be because private healthcare was easier to obtain, with no long waiting for treatment in Thailand's healthcare setting. Moreover, one-third of the participants have health insurance; their private hospital's costs may be covered by health insurance.

The neck (24.9%) was the most common site of severe discomfort. This was similar to a prior study that investigated in office workers (2). A recent study also revealed that the neck was the most frequent area for discomfort in

home computer users during the COVID-19 pandemic (19). This could imply that the most common discomfort area was not related to the workplace. Additionally, the majority of the participants (66.2%) in this study applied laptop computers which was similar to a current study (19). Because of the device's design, users have to flex their necks. Myofascial pain can be aggravated via muscle and spine imbalance. An ergonomic adjustment should be considered to reduce neck muscle activity.

Regarding the methods of treatment, the finding showed that conventional medicine (16.5%), CAM (23.7%), and both techniques (22.5%) were used. This corresponds to the outcome of Andarini's study, which was carried out in Indonesia (5). Probably because both countries have close cultural and behavioral aspects of seeking treatment for musculoskeletal pain. However, our study revealed CAM group was slightly higher than the conventional medicine group or both method groups, though receiving more than one method of treatment is also recommended by a guideline to be more effective than receiving only one (20,21). It was similar to the finding of Artus and colleagues which showed that using CAM in chronic musculoskeletal pain was more helpful (22). Based on affordability, socioeconomic, and community concept, CAM was chosen over conventional treatment in developing nations like our own (23).

Self-care is the initial step in pain management, and the majority of patients viewed it favorably (24). Even though a large percentage of them (53.1%) were in the group of those who had significant discomfort, we discovered that 95.8% of participants did not practice self-care. However, there was no statistical significance found in relation to healthcare utilization. Self-stretching exercises, using a hot pack, and adjusting one's own ergonomic position were considered to self-care activities in our study. These were active methods that some people might not preferred.

Although around half (52.1%) of them were experiencing severe conditions, the most frequent usage of healthcare was found to be infrequent (79.6%). In contrast, Nakamura's research on chronic musculoskeletal pain found that the most prevalent treatment frequencies

were once and many times a week, followed by once every 2 weeks or less and daily (25). This could be because we performed the questionnaire during the COVID-19 pandemic. Concerns about infection risk affected patients' receiving healthcare service significantly. The consequence of the situation caused substantial reductions in a wide range of healthcare activities (26). It was difficult to gain frequent access to the hospital. Though the frequency of contact with healthcare decreased during the pandemic, the significant factors related to healthcare utilization remained consistent with earlier studies.

Limitation

The investigation was conducted during the COVID-19 pandemic, hence access to hospitals was limited. This was a summary of the survey results. It was necessary to get specific information, such as hospital records. Physical discomfort was reported by the patient without any clinical evaluation data. Emotions might have an impact on the factor of discomfort. Further study should assess this parameter. Patient satisfaction, convenience of service access, treatment outcome, and ergonomic considerations of workstations should be incorporated for future research.

Our findings underscore the importance of our take-home message. The most prevalent severe discomfort area identified was the neck, emphasizing the significance of maintaining proper neck posture when using computers. Notably, the study reveals that short break durations, persistent and severe discomfort, and the widespread distribution of musculoskeletal discomfort among electronic device users working from home significantly impact the likelihood of seeking healthcare services.

CONCLUSIONS

Epidemiologic data have highlighted a distinct preference among individuals employing electronic devices at home and experiencing physical discomfort, favoring private healthcare options over government healthcare. Notably, the utilization of complementary and alternative medicine emerged as the favored treatment modality. Several key factors were identified as significantly linked to the uptake of

healthcare services, including an age threshold of 45 years, short break durations, the presence of chronic symptoms, the severity of discomfort, a higher number of discomfort areas, and the existence of ergonomic policies within organizations. These findings underscore the imperative for dedicated medical resources, encompassing both personnel and facilities, to cater to the needs of this specific patient population. Furthermore, optimizing work-break schedules and refining ergonomic policies holds promise for enhancing overall effectiveness.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

ADDITIONAL INFORMATION

Author Contribution

C.P.: conceptualization, methodology, writing - review & editing; P.N.: data curation, software, writing- original draft preparation W.D.: investigation, supervision

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Occupational Paraquat Exposure Cases Reported to the Ramathibodi Poison Center

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ABSTRACT

OBJECTIVE Paraquat (PQ) is a widely used non-specific herbicide. Paraquat poisoning both from intentional and unintentional exposure has been reported. The main objective of this study is to report on the characteristics, clinical effects, and outcomes of occupational PQ exposure reported to a poison control center in Thailand. The secondary objective is to determine factors associated with systemic toxicity from occupational PQ exposure.

METHODS This is a retrospective study of cases of occupational PQ exposure reported to the Ramathibodi Poison Center between January 2018 and December 2021.

RESULTS There were 124 PQ exposure cases during the study period, including 102 males and 22 females. Median age was 46 years (interquartile range 35.5-55.5 years). Routes of exposure included dermal (54.8%), inhalational (37.1%), and ocular (13.7%). Commonly used personal protective equipment (PPE) included trousers (18.5%), long-sleeve shirts (16.9%), and balaclavas (10.4%). Of the 68 dermal exposures, 23 (33.8%) reported having attempted skin decontamination prior to visiting the hospital. Systemic effects were reported in 22 cases (17.7%), including kidney injury (17.7%), hepatic injury (4.8%), and pulmonary injury (8.1%). All cases with systemic effects involved dermal exposures. Factors associated with systemic effects include mixing process, dermal exposure, lack of early skin decontamination, longer period between exposure and hospital visit, presence of wounds, body surface area involved and the grade of wounds.

CONCLUSIONS Occupational dermal PQ exposure can result in systemic effects. Individuals who handle PQ should be trained in and encouraged to practice safe PQ use, e.g., wearing personal protective equipment and using appropriate first aid measures if PQ exposure occurs.

KEYWORDS paraquat, occupational exposure, poison control center, paraquat toxicity

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INTRODUCTION

Paraquat (PQ) is a non-specific herbicide in the bipyridyl family. In plant chloroplasts, PQ

reacts with electrons from plastocyanin-ferredoxin oxidoreductase and oxygen (photosystem 1), resulting in superoxide radicals and cell

death (1). PQ is absorbed in the soil and degraded by microorganisms and photocatalytic degradation (2). PQ has been widely used for weed control due to its efficacy and relative environmental safety.

Toxicities in humans, due to both intentional and unintentional PQ exposures have been reported. Effects of PQ poisoning include irritation of exposed skin and mucous membranes, multiorgan dysfunction, pneumonitis, pulmonary fibrosis, and death (3,4). There is no effective specific antidote for PQ poisoning. To prevent PQ poisoning, PQ has been banned in some countries (5,6). In the United States, Australia, and New Zealand PQ applicators must be trained and certified (7,8).

In Thailand, paraquat has been banned since 1 June 2020 (9). PQ has been used in oil palm and rubber tree plantations as well as on corn, cassava, and sugar cane farms which are planted early in the Thai rainy season (10). PQ effectively controls weeds even when it rains within 15 to 30 minutes of spraying, which may explain the use of PQ in the rainy season (11). There have been training sessions for farmers on the use of pesticides both before and after the ban. Prior to the ban, farmers were required to be trained and certified by the Department of Agriculture to be allowed to purchase, possess, or use PQ (12). According to the Department of Agriculture, PQ users must wear personal protective equipment (PPE) including gloves, goggles, boots, respirators, long sleeve shirts, and trousers and must be covered with either a chemical resistant coverall suit, raincoat, or apron (13). There were 4,223 cases of PQ poisoning, including 1,950 deaths, reported to the Ramathibodi Poison Center (RPC) in the period 2010–2016. The majority of the PQ exposure cases reported to RPC were from intentional oral ingestion (14,15). When a hospital had a PQ exposure case, the primary care team could voluntarily consult the poison center for guidance on management.

Characteristics, clinical effects, treatment, and outcomes of occupational PQ exposure in Thailand have not been described. The main objective of this study is to report on the characteristics, clinical effects, and outcomes of occupational PQ exposure reported to a poison con-

trol center in Thailand. The secondary objective is to determine factors associated with systemic toxicity from occupational PQ exposure.

METHODS

Study setting

This retrospective observational study includes PQ exposures reported to RPC from January 2018 through December 2021. This study was approved by the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. RPC has provided a 24-hour hotline for nationwide toxicological consultation since 1996 (4). The consultation service is free of charge. Calls are received by specialists in poison information (SPIs), nurses or pharmacists with additional training in poison information service. Diagnoses of PQ exposure are based on history. There are medical toxicologist consultants available for complicated cases. Follow-up calls are made until recovery or a definitive outcome is reported. Calls are recorded in electronic database and the cases are reviewed and verified in daily staff meetings. Systemic treatment includes cyclophosphamide, dexamethasone, vitamin C, and vitamin E which are recommended in cases with systemic effects, and in cases with positive urine PQ screening by dithionite test. The final decision on management is made by the primary team taking care of the patient.

Definitions

Systemic effects were defined as the presence of at least one toxicity, including nephrotoxicity, hepatotoxicity, or pulmonary toxicity. The definition of nephrotoxicity was based on the RIFLE classification system for acute kidney injury (16). Hepatotoxicity was defined as an increase in aspartate aminotransferase or alanine aminotransferase levels greater than twice the normal upper limit. Pulmonary toxicity was defined as hypoxia or new pulmonary infiltration (17). Early decontamination was defined as decontamination within 1 hour following exposure.

Data collection

Case records were electronically abstracted using the active ingredient name coded as

“paraquat” and the manner of exposure as “occupational exposure”. All records were reviewed and verified by discussion among medical toxicologists and SPIs. Characteristics of patients, including age, sex, work activity related to exposure, route of exposure, contact area, wearing of PPE, clinical effects, treatment, and outcome of exposure were recorded. Characteristics were compared between cases with systemic effects and cases without systemic effects. If the primary team reported causes other than PQ for any of the clinical effects, those clinical effects were coded as “unrelated effects” and excluded from analysis.

Statistical analysis

Categorical data are presented as frequency and percentage. Continuous data is presented as median and interquartile range (IQR). Univariate analysis was used to determine the differences between cases with systemic effects and cases without systemic effects using the Wilcoxon rank-sum test for continuous variables and the chi-squared or Fisher’s exact test

for categorical variables. A p-value of less than 0.05 was defined as statistically significant.

RESULTS

During the study period there were 124 occupational PQ exposure cases reported to RPC, 102 males and 22 females (Table 1). Median age was 46 years (IQR 35.5–55.5 years). Systemic effects were reported in 22 cases (17.7%). The number of cases were highest in May and June, which is the early part of the rainy season (Figure 1). There was no difference in the number of cases among the reported years ($p = 0.235$ by Kruskal–Wallis test). The region with the highest number of cases was central region (46 cases, 37.1%).

Routes of exposures included dermal (54.8%), inhalational (37.1%), and ocular exposures (13.7%). All cases with systemic effects involved dermal exposures. One case with systemic effects involved both dermal and inhalational exposures. Spraying was the most common work activity related with exposure (108 cases, 86.4%). There was a higher proportion of expo-

Table 1. Characteristics occupational paraquat exposure cases reported to Ramathibodi Poison Center during 2018 to 2021

Characteristics	Number of cases (%)			p-value
	Total (124 cases)	Cases with systemic effect (22 cases)	Cases without systemic effect (102 cases)	
Male sex	102 (82.3)	21 (95.5)	81 (80.4)	0.120
Median age (years) (IQR)	46 (35.5–55.5)	47 (38–57)	46 (35–55)	0.552
Region				0.285
Central region	46 (37.1)	11 (50.0)	35 (34.3)	
Northern region	6 (4.8)	0	6 (5.9)	
North-eastern region	22 (17.7)	5 (22.7)	17 (16.7)	
Eastern region	16 (12.9)	2 (9.1)	14 (13.7)	
Western region	22 (17.7)	1 (4.55)	21 (20.6)	
Southern region	12 (9.7)	3 (13.6)	9 (8.8)	
Route of exposure*				
Dermal exposure	68 (54.8)	22 (100.0)	46 (45.1)	<0.001
Inhalational exposure	46 (37.1)	1 (4.6)	45 (44.1)	<0.001
Ocular exposure	17 (13.7)	0	17 (16.7)	0.041
Work process				0.043
Spraying	108 (87.1)	16 (72.7)	92 (90.2)	
Mixing	5 (4.0)	3 (13.6)	2 (2.0)	
Walking through sprayed area	4 (3.2)	1 (4.6)	3 (2.9)	
Not specified process	7 (5.7)	2 (9.1)	5 (4.9)	
Median duration between exposure to hospital visit (IQR)	1 d (4.5 hrs to 3 ds)	3 ds (2 ds to 5 ds)	1 d (4 hrs to 3 ds)	<0.001

*There were cases exposed to paraquat more than one route of exposure
IQR, interquartile range

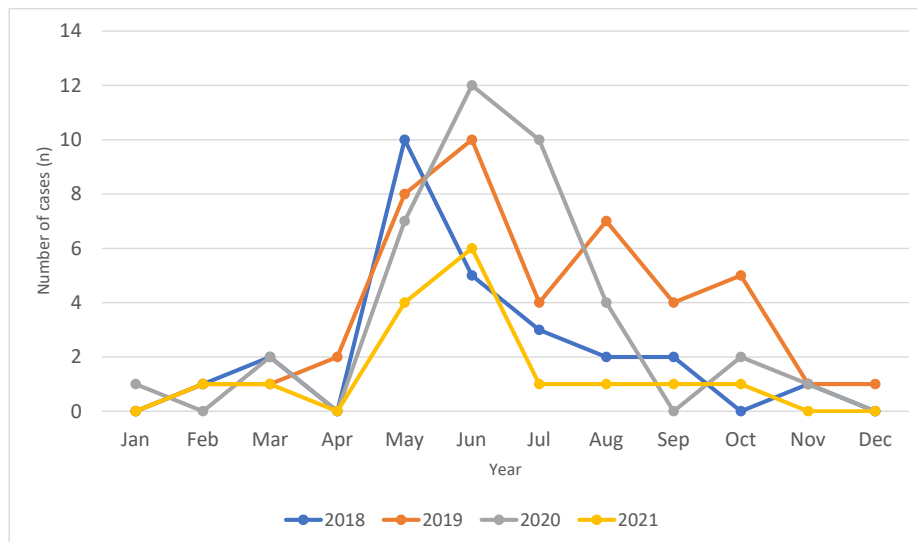


Figure 1. Number of Occupational paraquat exposure cases reported to Ramathibodi Poison Center during 2018 to 2021

Table 2. Personal protective equipment reported used in occupational paraquat exposure cases at Ramathibodi Poison Center from 2018 through 2021

Personal protective equipment reported used	Number of cases (%)			p-value
	Total (124 cases)	Cases with systemic effects (22 cases)	Cases without systemic effects (102 cases)	
Long sleeve shirt	21 (16.9)	2 (9.1)	19 (18.6)	0.362
Trousers	23 (18.6)	2 (9.1)	21 (20.6)	0.363
Balaclava	13 (10.5)	0	13 (12.8)	0.122
Cloth mask	6 (4.8)	1 (4.6)	5 (4.9)	1.000
Goggle	4 (3.2)	0	4 (3.9)	1.000
Gloves	12 (9.7)	2 (9.1)	10 (9.8)	1.000
Boots	10 (8.1)	2 (9.1)	8 (7.8)	1.000

sure during PQ mixing processes in cases with systemic effects (13.6% in cases with systemic effects, and 2.0% in cases without systemic effects). The median time from exposure to hospital visit was 1 day (IQR 4.5 hours to 3 days). Both dermal exposure and longer duration between exposure and hospital visit were associated with systemic effects ($p < 0.001$ for both factors). Commonly used PPE included trousers (18.5%), a long-sleeve shirt (16.9%), and balaclava (10.4%) (Table 2). No cases reported wearing a respirator, apron, raincoat, or coverall suit.

In dermal exposure cases, common contact areas included the perineum, legs, and back (38.3%, 13.3%, and 11.8% of the 68 dermal exposure cases, respectively) (Table 3). Twenty-three cases reported skin decontamination prior to hospital visits (33.8% of 68 cases). No instances of early skin decontamination were

associated with systemic effects ($p = 0.003$). Six cases reported eye decontamination prior to hospital visits (35.3% of 17 ocular exposures).

Wounds were the most common reported clinical effect (56 cases, 45.2%) (Table 4). Median area involved was 1% of the body surface area (IQR 1-2%, range 1-9%). Wound severity was reported as first degree burn in 24 cases, and second degree burn in 32 cases. Presence of wounds, involved body surface area, and grade of wounds were associated with systemic effects ($p < 0.001$ for all three factors). Systemic effects included kidney injury (22 cases, 17.7%), hepatic injury (6 cases, 4.8%), and pulmonary injury (10 cases, 8.1%) (Table 5).

Thirty-eight cases (30.6%) were admitted to hospital (Table 6). The median length of stay was 4 days (IQR 2-7 days, range 1-24 days). Cases with systemic effects had a higher admission rate and longer length of stay (both

Table 3. Dermal contact area and early skin decontamination of occupational paraquat exposure cases reported to Ramathibodi Poison Center from 2018 through 2021

Skin contact area	Number of cases (%)			p-value
	Total dermal exposure cases (68 cases)	Cases with systemic effects (22 cases)	Cases without systemic effects (46 cases)	
Face	3 (4.4)	0	3 (6.5)	1.000
Chest	3 (4.4)	0	3 (6.5)	1.000
Abdomen	2 (2.9)	0	2 (4.4)	1.000
Back	8 (11.8)	2 (9.1)	6 (13.0)	0.631
Arm	3 (4.4)	0	3 (6.5)	1.000
Hand	7 (10.3)	2 (9.1)	5 (10.9)	0.606
Perineum	26 (38.3)	8 (36.6)	18 (39.3)	0.079
Buttock	6 (8.8)	2 (9.1)	4 (3.9)	0.288
Thigh	1 (1.5)	1 (4.6)	0	0.177
Leg	9 (13.3)	4 (18.2)	5 (10.9)	0.052
Foot	5 (7.4)	2 (9.1)	3 (6.5)	0.215
Early skin decontamination*	23 (33.8)	2 (9.1)	21 (45.7)	0.003

*Includes removing of contaminated clothes (if any) and washing the contaminated skin within 1 hour after exposure

Table 4. Clinical effects of occupational paraquat exposure in cases reported to Ramathibodi Poison Center from 2018 through 2021

Clinical effects	Number of cases (%)			p-value
	Total (124 cases)	Cases with systemic effects (22 cases)	Cases without systemic effects (102 cases)	
Wound	57 (46.0)	20 (90.9)	37 (36.3)	< 0.001
Wound grading				< 0.001
First degree burn	25 (20.2)	2 (9.1)	23 (22.6)	
Second degree burn	32 (25.8)	18 (81.8)	14 (13.7)	
Wound area				< 0.001
1% of body surface area (BSA)	33 (26.6)	9 (40.9)	24 (23.5)	
2% BSA	12 (9.7)	4 (18.2)	8 (7.8)	
3% BSA	9 (7.3)	4 (18.2)	5 (4.9)	
More than 3% BSA	3 (2.4)	3 (13.6)	0	
Nausea	22 (17.7)	1 (4.6)	21 (20.6)	0.120
Dizziness	22 (17.7)	0	22 (21.6)	0.013
Eye irritation	17 (13.7)	0	17 (16.7)	0.041
Vomiting	14 (11.3)	1 (4.6)	13 (12.8)	0.460
Fatigue	11 (8.9)	0	11 (10.8)	0.210

Table 5. Systemic effects of occupational paraquat exposure cases reported to Ramathibodi Poison Center from 2018 through 2021

Systemic effects	Number of cases (%)	
	Total (124 cases)	Cases with systemic effects (22 cases)
Nephrotoxicity	22 (17.7)	22 (100.0)
Hepatotoxicity	6 (4.8)	6 (27.3)
Pulmonary toxicity	10 (8.1)	10 (45.5)

$p < 0.001$). Local treatment included wound dressing, dermal irrigation, and eye irrigation. Common specific treatment included IV dexamethasone (16.1%), IV vitamin C (15.3%), oral vitamin E (14.5%), and IV cyclophosphamide (12.9%). There were 8 deaths, all of which involved dermal exposure, lack of early skin decontamination, delayed hospital visit (range 2–8 days after exposure), and systemic effects.

Urine PQ screening by dithionite test was performed in 22 cases. Of those, four cases had

Table 6. Clinical effects of occupational paraquat exposure in cases reported to Ramathibodi Poison Center from 2018 through 2021

Treatment	Number of cases (%)			p-value
	Total (124 cases)	Cases with systemic effects (22 cases)	Cases without systemic effects (102 cases)	
Hospital admission	38 (30.7)	22 (100.0)	16 (15.7)	< 0.001
length of stay (days) (IQR)	4 (2-7)	6.5 (4-12)	2.5 (2-3)	0.001
Eye irrigation	16 (12.9)	0	16 (15.7)	0.073
Skin irrigation	14 (11.3)	3 (13.6)	11 (10.8)	0.713
Wound dressing	55 (44.4)	20 (90.9)	35 (34.3)	< 0.001
Endotracheal intubation and ventilation support	4 (3.23)	4 (18.2)	0	0.001
Oxygen supplement	6 (4.8)	6 (27.3)	0	< 0.001
Intravenous fluid	41 (33.1)	20 (90.9)	21 (20.6)	< 0.001
Antibiotic	36 (29.3)	16 (76.2)	20 (19.6)	< 0.001
Antihistamine	17 (13.7)	3 (13.6)	14 (13.7)	1.000
Antiemetic	9 (7.3)	1 (4.6)	8 (7.8)	1.000
Cyclophosphamide	16 (12.9)	15 (68.2)	1 (0.1)	< 0.001
Dexamethasone	20 (16.1)	17 (77.3)	3 (2.9)	< 0.001
Vitamin C	19 (15.3)	17 (77.3)	2 (2.0)	< 0.001
Vitamin E	18 (14.5)	16 (72.7)	2 (2.0)	< 0.001
N-acetylcysteine	4 (3.23)	3 (13.6)	1 (1.0)	0.018

IQR, interquartile range

positive urine PQ screening results. Screening was performed at 1 day (1 case), 2 days (2 cases) and 3 days (3 cases) after exposure. All four were cases of dermal PQ exposure. Three cases with a positive urine PQ screening had systemic effects. One case with a positive urine PQ screening who received systemic treatment for 4 days had no systemic effects. There were 18 cases with negative urine PQ screening, including 5 cases with systemic effects and 13 cases without systemic effects. In the cases with systemic effects with negative urine PQ screening results, the urine PQ screening tests had been performed 1-3 days after exposure. In cases without systemic effects who had negative urine PQ screening, urine PQ screening tests were performed at between 3 hours and 4 days after exposure.

DISCUSSION

This article describes occupational PQ cases reported to a poison control center (RPC) in Thailand. Most cases were reported early in the rainy season. The majority of cases were males of working age, which is consistent with previous studies on occupational pesticide exposure (10,18). Despite PQ being banned since 1 June

2020, no difference was found in the number of occupational PQ exposure cases between years before and after the ban. One possible reason is that there may have been quantities of PQ remaining in the country after the ban. Previous studies in Korea, Taiwan, and Sri Lanka found a decrease in suicide using pesticides including paraquat after banning (6,19,20). The total number of cases of occupational PQ poisoning and pesticide-related suicide in Thailand should be monitored to determine the effect of the ban.

In this study, reported PPE use rates were found to be quite low, consistent with a previous study of occupation carbamate poisoning in Thailand (18). The PPE use rates in our study are lower than those in a voluntarily survey of healthy farmers (21); that difference may be explained by a difference in the study populations. That there was no association between PPE use and systemic effects in our study may be explained by 1) a low rate of PPE use, 2) no reports of wearing a chemical protective coverall suit, raincoat, or apron which can largely prevent PQ absorption to inner-layer clothing and skin. A study of urine and dermal PQ concentrations in PQ sprayers reported that using PPE was associated with lower dermal PQ exposures (22).

Individuals applying dangerous herbicides and pesticides should be trained and encouraged to use PPE and their PPE use should be monitored. Thai farmers should wear PPE as suggested by Department of Agriculture (13).

In our study, systemic effects were reported in cases with dermal exposure. Dermal PQ exposures have been reported to cause systemic effects (23,24). PQ absorption is higher in damaged skin and with prolonged contact (25). PQ can cause irritation and burns on contacted skin, which can enhance absorption (25). We found that early skin decontamination (within 1 hour) helps prevent systemic effects. A previous study reported that early skin decontamination can decrease dermal penetration of toxic chemicals (26). The grade and area of a wound and the length of time between exposure and health care are related to PQ systemic effects. Inflamed or broken skin is also associated with higher PQ absorption. Wound severity may reflect contact time, PQ concentration, and area of exposure. Early decontamination and evaluation by a healthcare provider should be emphasized in training of PQ handlers. Clean water should be available in the workplace for prompt dermal and ocular decontamination.

In this study, systemic effects were not reported in any cases with no dermal exposure. Inhalation exposure and ocular exposure did not result in systemic effects. PQ is less likely to evaporate at room temperature due to its low vapor pressure (0.000001 mmHg) (25,27). More than 98% of sprayed PQ has a droplet size larger than 7 micrometers, which can be retained in the upper airway, preventing alveolar deposition and absorption (28). Sprayed PQ also has a lower concentration than PQ prior to mixing or diluting, which may explain the lower proportion of systemic effects in cases of spraying (25). PQ concentration during contact may also explain the higher proportion of cases with systemic effects occurring during the mixing process. Eye irritation from PQ and dizziness resulting from the strong odor may cause a farmer to stop working and thus reduce further PQ exposure. This may explain why most reports of eye irritation and dizziness are in cases without systemic effects.

Currently there is no effective antidote for PQ toxicity. Common systemic treatments include a combination of steroids, anti-inflammatory drugs, and antioxidants (3,4). Due to rapid distribution of PQ into tissues, significant quantities of serum PQ can be removed by early hemodialysis and hemoperfusion, i.e., within the first few hours after ingestion (3). Delayed enhance elimination does not change the prognosis of PQ poisoning. In this study, there were no cases that underwent hemodialysis or hemoperfusion. Most of the cases in our study, especially those with systemic effects, presented at the healthcare facility more than 4 hours after exposure. Further study of the kinetics and role of enhanced elimination of dermal PQ exposure is needed to evaluate the role and limitations of enhanced elimination in cases of dermal PQ exposure.

In our study, there were 5 cases with systemic effects that had had a negative urine PQ screening test. In each of those cases, the screening test had been done later than 24 hours after exposure. After ingestion, 90% of the absorbed PQ is excreted in urine within 12–24 hours (29). Urine PQ screening using the sodium dithionite test can predict PQ toxicity if performed within 12 hours following ingestion (4,29). To the best of our knowledge, there have been no studies to evaluate the efficacy of using the urine dithionite test to determine the risk of PQ toxicity resulting from dermal exposure. Further study is needed to evaluate the role of the urine sodium dithionite test in cases of dermal PQ exposure. PQ handlers should be advised to visit a healthcare facility for evaluation as soon as possible after dermal PQ exposure.

As a retrospective study of voluntarily reported data, this study has some limitations. The study was affected by selective bias. The majority of RPC calls were from healthcare providers, which tend to be more severe than cases in survey studies. For the same reason, the cases in this study may not reflect all the occupational PQ exposures in Thailand. The extent of PPE use in this study includes only cases exposed to PQ, so it may be lower than the average of PPE use by all farmers. This study is based on the Thai setting. Studies in other countries may have different findings due to

differences in regulations, product availability, and health systems.

CONCLUSIONS

Based on data from one poison control center, occupational dermal PQ exposure can result in both local and systemic effects. There were no systemic effects reported from occupational inhalational or ocular PQ exposure in this study. There is a low rate of PPE use in PQ exposure cases. Factors associated with systemic effects include exposure during the PQ mixing process, dermal exposure, lack of early skin decontamination after exposure, a longer duration between exposure and hospital visit, the presence and grade of wounds and the body surface area involved. PQ handlers should be trained on and encouraged to practice safe use of PQ, to wear personal protective equipment, and to seek first aid after PQ exposure.

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CONFLICTS OF INTERESTS

The authors have no conflicts of interest to report.

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