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順天堂醫事雜誌

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順天堂醫事雜誌

The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雜誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雜誌), *Juntendo Igaku Zasshi* (順天堂医学雜誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雜誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intension, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雜誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) in 1887 to the present.

出典：小川秀興（OGAWA Hideoki, M.D., Ph.D.）：順天堂醫事雜誌（Juntendo Medical Journal）2013；59：6-10.

本誌は昭和39年（1964年）から平成24年（2012年）末まで『順天堂医学』として刊行されてきた．しかし，その起源は明治8年（1875年）から10年（1877年）にかけて発刊された日本最古の医学誌『順天堂醫事雜誌』（計8巻）にある．さらに明治18年（1885年）から19年（1886年）まで，会員限定配本として順天堂醫事研究會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』が明治20年（1887年）に官許を受けて公刊されたので，順天堂ではこれを通刊1号としてきた．以来，『順天堂醫事研究会雜誌』，『順天堂医学雜誌』，『順天堂医学』と名称を変更して刊行されてきた．

今般，順天堂が創立175周年を迎える平成25年（2013年）の59巻1号を期して，本来の名称である『順天堂醫事雜誌』と復刻し，その起源である明治8年（1875年）第1巻をもって創刊号（通刊第1号）とすることとした．従来の巻号と欧文誌名は，昭和30年（1955年）1月10日発行のものを1巻1号としており，欧文誌名もこれより付け始めたもので不本意であるが，混乱を避けるためにこれらを継承する．ただし，通刊数は明治8年（1875年）から19年（1886年）にかけて刊行された『順天堂醫事雜誌』8巻分と順天堂醫事研究會の雑誌『報告』39集，計47巻分を通巻834号に加え，59巻1号を通刊882号とした．

出典：小川鼎三，酒井シヅ：順天堂医学　1980；26：414-418.
小川秀興：順天堂醫事雜誌　2013；59：6-10.

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From the illustrator: Halloween is just around the corner, and many pumpkins with unique patterns and shapes are displayed at the flower shop. They are actually all real pumpkins. Recently, Halloween event has become popular in Japan, so, I feel like drawing pumpkins.

Reviews

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Mechanism of Post-stroke Axonal Outgrowth and Functional Recovery

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Axonal outgrowth after stroke plays an important role in tissue repair and is critical for functional recovery. In the peri-infarct area of a rat middle cerebral artery occlusion model, we found that the axons and dendrites that had fallen off in the acute phase of stroke (7 days) were regenerated in the chronic phase of stroke (56 days). *In vitro*, we showed that phosphatase tensin homolog deleted on chromosome 10/Akt/Glycogen synthase kinase 3β signaling is implicated in postischemic axonal regeneration. In a rat model of chronic cerebral hypoperfusion, oral administration of L-carnitine induced axonal and oligodendrocyte regeneration in the cerebral white matter, resulting in myelin thickening, and it improved cognitive impairment in rats with chronic cerebral ischemia. Recently, it has been shown that exosomes enhanced functional recovery after stroke. Exosome treatment has less tumorigenicity, does not occlude the microvascular system, has low immunogenicity, and does not require a host immune response compared to conventional cell therapy. Several studies demonstrated specific microRNA in exosomes, which regulated signaling pathways related to neurogenesis after stroke. Collectively, there are various mechanisms of axonal regeneration and functional recovery after stroke, and it is expected that new therapeutic agents for stroke with the aim of axonal regeneration will be developed and used in real-world clinical practice in the future.

Key words: stroke, axonal outgrowth, semaphorin 3A, exosomes, functional recovery

Introduction

Stroke is the leading cause of disability worldwide[1)]. In Japan, about 1.2 million people had strokes, and it is the fourth leading cause of death. In addition, medical expenses for stroke account for 11% in elderly persons, and they are expected to increase further in Japan, because Japan is facing a 'super-aged' society.

Ischemic stroke accounts for about 80% of all ischemic stroke cases, and it has a variety of mechanisms[2, 3)]. In recent years, stroke medical care has made dramatic progress due to the spread of intravenous alteplase and intravascular thrombectomy for acute ischemic stroke, as well as the development of preventive medicine due to the emergence of various new antithrombotic drugs. However, once a stroke develops and severe disability occurs due to failure of such acute treatments, the burden on the patient and family is immeasurable. So far, sorts of agents have been tried and shown as effective for neuroprotection against ischemia in preclinical studies. However, these agents failed to show efficacy and safety in human stroke[4)]. Thus, there is an urgent need to develop alternative novel therapies that can facilitate functional recovery based on neuroregeneration.

Post-stroke axonal outgrowth is fundamentally related to recovery from functional impairment after stroke, and the several mechanisms have been

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elucidated[5,6]. In this paper, the results of our experimental research on axonal regeneration after stroke are reviewed.

Molecular mechanisms including microRNA for axonal outgrowth

Peripheral sensory neurons activate a pro-regenerative program after nerve injury to enable axon regeneration and functional recovery. In contrast, regeneration of axons is poor in the central nervous system after injury. It is thought that there are various factors that inhibit axon regeneration, including Nogo, myelin-associated glycoprotein, oligodendrocyte-myelin glycoprotein, chondroitin sulfate proteoglycans present in injured scar tissue, and extracellular matrices such as semaphorin 3A[7,8]. On the other hand, there is an endogenous cAMP-mediated signal that regenerates axons after injury in neurons[9,10].

An increasing number of studies have found that microRNA is involved in axonal growth[11,12]. In superior cervical ganglia neurons, miR-338 locally regulates mitochondrial activity in axons[12]. It was shown that attenuation of miR-9 in embryonic cortical neurons facilitated axonal outgrowth by targeting microtubule-associated protein 1b[11]. The miR-17-92 cluster is a typical highly conserved polycistronic miRNA cluster, which is located in human chromosome 13, encoding six mature miRNAs: miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92a[13]. The miRNA-17-92 cluster may be highly expressed in a wide range of tumor cells and types of cancer, such as lung, breast, pancreatic, prostate, and thyroid cancers, and lymphomas[14]. We focused on the miR-17-92 cluster and investigated whether the miR-17-92 cluster enhances axonal outgrowth in primary cultured neurons. We found that the miR-17-92 cluster was expressed in the distal axons of the neurons. Overexpression of the miR-17-92 cluster in cortical neurons significantly increased axonal outgrowth, whereas distal axonal attenuation of endogenous miR-19a suppressed axonal outgrowth. Overexpression of the miR-17-92 cluster reduced Phosphatase and Tensin Homolog Deleted from Chromosome 10 (PTEN) (PTEN) proteins and elevated phosphorylated mammalian target of rapamycin (mTOR) in the distal axons. In contrast, distal axonal attenuation of miR-19a increased PTEN and inactivated mTOR in the axons, but alterations of these proteins were not prominent in the cell bodies. Thus, we showed that axonal alteration of miR-17-92 cluster expression enhanced axonal outgrowth with regulation of PTEN/mTOR signaling[15].

Post-stroke axonal-outgrowth in the peri-infarct area

Many stroke patients show some degree of functional recovery a few months after their stroke event, which is related to post-stroke axonal outgrowth. Axonal outgrowth has been studied in experimental stroke models. The stroke induces sprouting of axons from contralateral cortex into the ipsilateral red nucleus[16] and the ipsilateral cervical spinal cord[17,18].

In the peri-infarct area, which is an area from the margin of the ischemic core to 300 μm from the ischemic core in the middle cerebral artery occlusion model (MCAO), there could be plasticity that induces reconstruction of the neural networks and brain repair after stroke injury[19,20]. It has been shown that ATRX and GDF10 are related to axonal regeneration in the peri-infarct area[5,21]. In our previous study, we evaluated axonal outgrowth in the peri-infarct area from the acute to chronic phases of ischemia[6]. The expression of phosphorylated neurofilament heavy chain (pNFH), a marker for axons, decreased on the 7th day of MCAO, but it increased substantially to the chronic phase on the 28th and 56th days after MCAO. Moreover, $pNFH^+$ axons were myelinated by oligodendrocytes. Regeneration of dendrites and dendritic spines was also observed 56 days after MCAO. In cultured cortical neurons, we analyzed the pNFH levels by western blotting after oxygen-glucose deprivation (OGD) for 3 h which was *in vitro* model of acute ischemic stroke. We found a substantial increase in pNFH levels 96 hours after OGD, which corresponds to the chronic stage of cerebral infarction, together with downregulation of PTEN and upregulation of phosphorylated Akt and phosphorylated glycogen synthase kinase 3β (GSK-3β). Administration of an Akt inhibitor after OGD resulted in decreased expression of pAkt, downstream pGSK-3β, and pNFH, whereas administration of a GSK-3 inhibitor decreased expression of pGSK-3β and increased expression of pNFH. In the peri-infarct area, pGSK-3β+ fibers were co-localized with

pNFH+ fibers in a rat MCAO model. Collectively, we found that axonal outgrowth is regulated through PTEN/Akt/GSK-3β signaling after stroke[6].

Axonal navigation was facilitated by several guidance molecules with attractive and repulsive signals on their growth cones. Reactive astrocytes form glial scars that hinder axonal regeneration in the peri-infarct area[22]. On the contrary, it was shown that glial scars are essential for axonal regeneration after spinal cord injury[23]. Semaphorins are a large family of guidance cue proteins, and semaphorin 3A (Sema3A) is a secreted protein that has been shown to inhibit axonal growth. After spinal injuries and optic nerve axotomy, Sema3A is implicated in scar formation[8, 24]. Sema3A is also expressed in ischemic neurons after stroke[25]. A previous study showed that inhibition of Sema3A enhanced axonal regeneration and improved functional recovery after spinal cord injury[8]. In Sema3A signaling, downstream of Sema3A through the NRP1/PlexA1 complex, Rnd1 and R-Ras are linked with Akt/GSK-3β signaling. Thus, we had sought to analyze whether inhibition of Sema3A regulated Rnd1/R-Ras/Akt/GSK-3β signaling and axonal outgrowth after ischemia. Using cortical neurons *in vitro*, the sema3A inhibitor downregulated Rnd1 and upregulated R-Ras, which in turn activated Akt and pGSK-3β, increasing pNFH after OGD. It was found that pGSK-3β was co-localized with pNFH axons. In a rat MCAO model, expression of Sema3A in neurons increased in the acute phase of stroke, reached a peak at 14 days, and then decreased to 56 days after MCAO. We administered a sema3A inhibitor into the peri-infarct area using an osmotic mini-pump. A high dose of the sema3A inhibitor significantly increased $pNFH^+$ axons and neuronal GSK-3β in the peri-infarct cortex, and it enhanced functional recovery during the recovery period in a rat MCAO model[26].

L-carnitine improves cerebral white matter injury and cognitive impairment

Ligation of bilateral common carotid arteries (LBCCA) induces chronic cerebral hypoperfusion, which results in cerebral white matter injury and cognitive impairment in rats, and is a model of vascular dementia. Administration of edaravone for three consecutive days after LBCCA upregulated eNOS levels in endothelial cells in the cerebral white matter and ameliorated white matter injury 28 days after LBCCA[27].

L-carnitine has potent antioxidant and anti-inflammatory effects, and it has been reported to improve intermittent claudication in patients with peripheral arterial disease and to promote myocardial remodeling in patients with acute myocardial infarction[28, 29]. As for the therapeutic effect of L-carnitine on cerebral infarction, it has been reported that L-carnitine suppressed the loss of neurons due to its antioxidant effect in a rat model of transient cerebral ischemia[30]. In our previous study, 600 mg/kg of L-carnitine daily were administered orally to rats subjected to LBCCA for 28 days. L-carnitine-treated rats showed a significant reduction of escape latency in the Morris water maze task 28 days after LBCCA. On western blot analysis using samples of corpus callosum, L-carnitine increased protein levels of pNFH, together with a reduction in phosphorylated PTEN, and it increased phosphorylated Akt and mammalian target of rapamycin (mTOR) 28 days after LBCCA. On immunohistochemistry, L-carnitine suppressed lipid peroxidation and oxidative DNA damage, and it enhanced oligodendrocyte marker expression and myelin sheath thickness after LBCCA. The regulation of the PTEN/Akt/mTOR signaling pathway by L-carnitine enhanced axonal plasticity while ameliorating oxidative stress and increasing oligodendrocyte myelination of axons. Thus, L-carnitine improved white matter lesions (WMLs) and cognitive impairment in a rat chronic hypoperfusion model[31].

Exosomes as a therapy for stroke recovery

Exosomes, extracellular vesicles that are 40 to 100 nm in diameter, and enriched in microRNA, mRNA, nucleic acids, lipids, and proteins, exert intercellular communication in CNS not only under normal physiological conditions, but also under pathological conditions[32-34]. Exosome treatment is superior to cell therapy because: (1) it has less tumorigenicity; (2) it does not occlude the microvascular system; (3) it has low immunogenicity not requiring a host immune response; and (4) tough lipid bilayer vesicles retain bioactivity[34-37]. Treatment with exosomes has been proven to be a good candidate for not only myocardial injury, but also kidney injury, by suppressing the inflammatory

reaction and oxidative stress, and enhancing repair of injured tissues[38–43].

In the central nervous system, exosomes exert important roles in cell–cell communication in brain remodeling after stroke[34]. It has been shown that exosomes derived from mesenchymal stromal cells (MSCs) in stroke treatment displayed the same tissue regeneration capability as MSCs themselves, and other studies demonstrated that treatment with such exosomes enhanced not only neurogenesis, angiogenesis, and axonal outgrowth, but also suppression of inflammatory reactions[44–47]. It was demonstrated that prion proteins in astrocyte-derived exosomes increased after ischemia, which exerted neuroprotection *in vitro*[48]. Xin et al showed that administration of MSC-derived exosomes with high enrichment of miR-133b facilitated the release of astrocyte-derived exosomes, which increased neurite outgrowth[49]. Polarization of microglia induced by IL-4 increased miR-26a in microglia-generated exosomes, which may promote tube formation *in vitro* and angiogenesis *in vivo* after ischemia[50]. In our previous study, inhibition of Sema3A in ischemic astrocytes downregulated miR-30c-2-3p and miR-326-5p in astrocyte-derived exosomes, which had the capability of promoting axonal elongation in ischemic neurons with upregulation of prostaglandin D2 synthase[32].

Conclusions

There is an urgent need to develop novel therapies to enhance functional recovery based on axonal outgrowth. The inhibition of inhibitory molecules for axonal outgrowth and exosomes can be a new therapeutic candidate for stroke recovery.

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Author contributions

YU-Drafting the manuscript, study concept, acquisition of data, supervision and coordination, and reading and approving the final manuscript.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

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Original Articles

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Pharmacotherapy in Patients with Alzheimer-type Dementia Presenting with Behavioral and Psychological Symptoms of Dementia: A Retrospective Chart Review of 102 Patients Available for 12-month Follow-up after Initiation of Treatment

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Objective: Alongside non-pharmacological intervention, pharmacotherapy particularly with atypical antipsychotics is assumed to be effective for behavioral and psychological symptoms of dementia (BPSD).

Methods: This retrospective study investigated the effectiveness and safety of pharmacotherapy including antipsychotics in outpatients or inpatients with BPSD.

Results: Of all Alzheimer-type dementia (AD) patients with BPSD initiating treatment between March and August 2011, a total of 102 patients available for 12-month follow-up comprised the subjects in this chart review. Of these, 68 (66.7%) continued treatment in the ambulatory or inpatient setting, with their MMSE scores improved from 17.3 ± 3.6 at baseline to 18.3 ± 3.53, 17.9 ± 3.80 and 17.0 ± 4.14 after 3, 6 and 12 months, respectively. In contrast, their NPI scores were significantly different from 11.7 ± 11.2 at baseline to 4.86 ± 5.40, 3.56 ± 4.65 and 2.27 ± 3.77 after 3, 6 and 12 months, respectively. Of the 36 inpatients available for follow-up, 27 (75%) on concurrent antipsychotics (chlorpromazine [CP] equivalent, 162.2 mg) at baseline remained on concurrent antipsychotics (CP equivalent, 212.5 mg) after 12 months, while, of the 66 outpatients available for follow-up, 13 (19.7%) on concurrent antipsychotics (CP equivalent, 93.4 mg) at baseline remained on concurrent antipsychotics (CP equivalent, 113.0 mg) after 12 months.

Conclusions: Study results confirmed the effectiveness and safety of the study treatment in Japanese AD patients with BPSD for up to 12 months. How best to incorporate antipsychotics into the treatment of BPSD in clinical settings lies in the hands of us Japanese clinicians.

Key words: Acetylcholinesterase inhibitor, atypical antipsychotic agents, Alzheimer-type dementia, behavioral and psychological symptoms of dementia, pharmacotherapy

Introduction

Now that dementia has emerged as an urgent issue to be addressed with the number of hospitalized patients with dementia was approximately 75,800 in 2020 in Japan[1], clinical psychiatrists are often called on to treat not only cognitive dysfunction but also behavioral and psychological symptoms of dementia (BPSD) in patients with Alzheimer-type dementia (AD). BPSD dates back to 1838 when Esquirol defined senile dementia as inclusive of a subtype associated with concomitant emotional disturbance. Only in the 1980s did BPSD become the focus of intensive study. As a consequence, BPSD were assumed to lead to untoward consequences, such as early institutionalization,

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increased medical costs, decreased quality of life (QOL) of both affected patients and their caregivers, increased stress and excessively impaired performance on the part of their caregivers[2]. BPSD are reported in many studies to affect a maximum of 97% of dementia patients in nursing homes and communities and to occur with the progression of their dementing illness and highly frequently during a specific period of time[3]. While, generally, non-pharmacological intervention represents a first treatment of choice for BPSD, BPSD are deemed an indication for pharmacotherapy combined with a non-pharmacological intervention when they are thought likely to adversely affect the QOL of both affected patients and their caregivers or raise safety concerns. However, the US Food and Drug Administration (FDA) issued a warning in April 2005 that elderly dementia patients receiving atypical antipsychotics are at 1.6- to 1.7-fold risk of death compared to those receiving placebo[4]; as a consequence, the clinical trials of antipsychotics then underway to obtain an indication for BPSD were all discontinued, with the result that, to date, no drugs are available for the treatment of BPSD.

Against this background, therefore, the authors investigated the effectiveness and safety of pharmacotherapy in dementia patients presenting with BPSD in a clinical setting.

Materials and Methods

This study was deemed exempt from review by the institutional review board of Hasegawa Hospital, Tokyo, Japan as involving only chart reviews and related statistical analyses, with the need to obtain informed consent waived due to the use of anonymized data involving no more than minimal risk to the subjects in this study.

Of all outpatients and the new inpatients with AD treated at Hasegawa Hospital from March and August, 2011, all AD patients newly initiating pharmacotherapy who were available for 12-month follow-up by medical charts were included to retrospectively assess improvements in cognitive symptoms as core symptoms of AD, BPSD, medication adherence, and (reasons for) mediation discontinuation, for 12 months. Outcome measures included: Mini-Mental State Examination (MMSE) for cognitive function; and Neuropsychiatric Inventory (NPI) for BPSD[5]. On the assumption that the focus should be placed on the assessment of BPSD as incurring a heavier burden on families and caregivers in this study than other outcomes, the study was conducted with NPI as its primary outcome measure, and MMSE, medication adherence and tolerability as its secondary outcome measures. During the study, all patients received galantamine as the only AChEI, but they were also allowed, as the need arose, to concurrently receive any suitable psychotropic agent, except for any other AChEI. A part of patients (18/102, 17.6%) was treated with memantine 10-20 mg/day during the course of the study. At the 12 month, the average dosage of memantine was 18.1 ± 4.0 mg/day (n= 16). The background characteristics of the patients were also explored for their relationship with their course of treatment. All patients had been fully explained about the risks and benefits of the off-label use of psychotropic agents, so that any such psychotropic agent was available for use as needed in patients who gave written informed consent. Patients were judged eligible for study entry if they were diagnosed with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for the clinical diagnosis of AD[6] or if they met the operational diagnosis of AD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[7]. For statistical analyses, logistic regression model was used. To examine the changes of MMSE and NPI scores between the baseline and each time point, paired t-test was used. In all statistical comparisons, the significance level (two-tailed) was established at $\alpha = 0.05$.

Results

Of all AD patients initiating treatment during the period between March and August 2011, a total of 102 patients were available for 12-month follow-up by medical chart review. The subjects consisted of 36 men and 66 women who had a mean age of 77.7 years (men/women, 76.7/78.2 years), a mean (SE) baseline MMSE score of 17.3 (3.6) and a mean baseline NPI score of 11.7 (11.2) (Table 1). Of all subjects, 68 (66.7%) continued with the treatment in the ambulatory or inpatient setting during the 12-month follow-up (Table 2). Their MMSE scores

Table 1 Patient characteristics (n = 102)

No. of men/women	36/66
Mean age	77.7 years (men, 76.7; women, 78.2)
No. of inpatients/outpatients	36/66
No. of patients with/without complications	67/35
No. of patients with/without prior AD drug use	57 (donepezil, 56; rivastigmine, 1)/45
Baseline MMSE score (mean ± SE)	17.29 ± 3.6
Baseline NPI score (mean ± SE)	11.7 ± 11.2

MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory

Table 2 Changes in outcome measures and number of patients on treatment

		Baseline	3 months	6 months	12 months
MMSE	Inpatients	17.94	19.31	19.83	19
	Outpatients	16.97	17.74	17.07	16.118
NPI	Inpatients	17.47	5.64	3.88	3.72
	Outpatients	8.35	4.44	3.44	1.76
No. of patients on treatment	Inpatients	36	18	15	13
	Outpatients	66	75	64	55

MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory

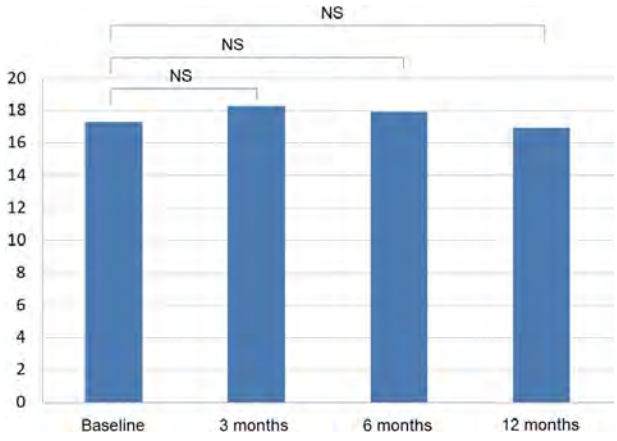

Figure 1 Changes in MMSE scores during follow-up

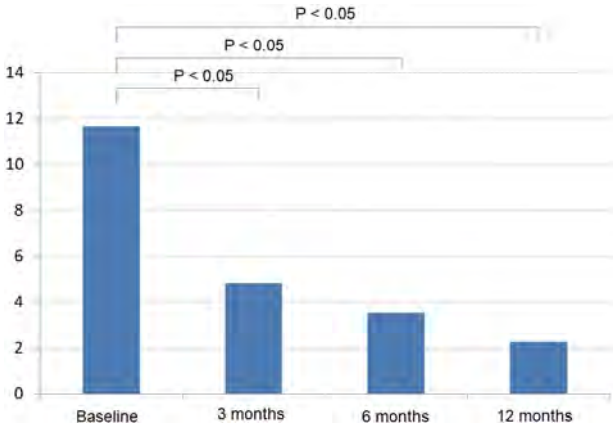

Figure 2 Changes in NPI scores during follow-up

at baseline was 17.3 ± 3.6 and 18.3 ± 3.53, 17.9 ± 3.80 and 17.0 ± 4.14 after 3, 6 and 12 months of treatment, respectively. Their MMSE scores were not significantly different from baseline at any of the time points evaluated (Figure 1). In contrast, their NPI scores were significantly different at 4.86 ± 5.40, 3.56 ± 4.65 and 2.27 ± 3.77 after 3, 6 and 12 months of treatment, respectively from baseline (11.7 ± 11.2) ($P < 0.05$, paired t-test) (Figures 2, 3, 4).

Of the 36 inpatients available for follow-up, 27 (75%) had been receiving concurrent antipsychotics (chlorpromazine [CP] equivalent, 162.2 mg) at baseline, which included aripiprazole (45%), quetiapine (21%), olanzapine (14%), risperidone extended-release injection (10%), paliperidone (7%) and risperidone (3%), while 8/13 (61.5%) were receiving concurrent antipsychotics (CP equivalent, 212.5 mg) after 12 months of treatment, which included aripiprazole (75%) and paliperidone (25%).

In contrast, of the 66 outpatients available for follow-up, 13 (19.7%) had been receiving concurrent antipsychotics (CP equivalent, 93.4 mg) at baseline, which included aripiprazole (74%), quetiapine (9%), and olanzapine (17%), while 14/55 (25.5%) were receiving concurrent antipsychotics

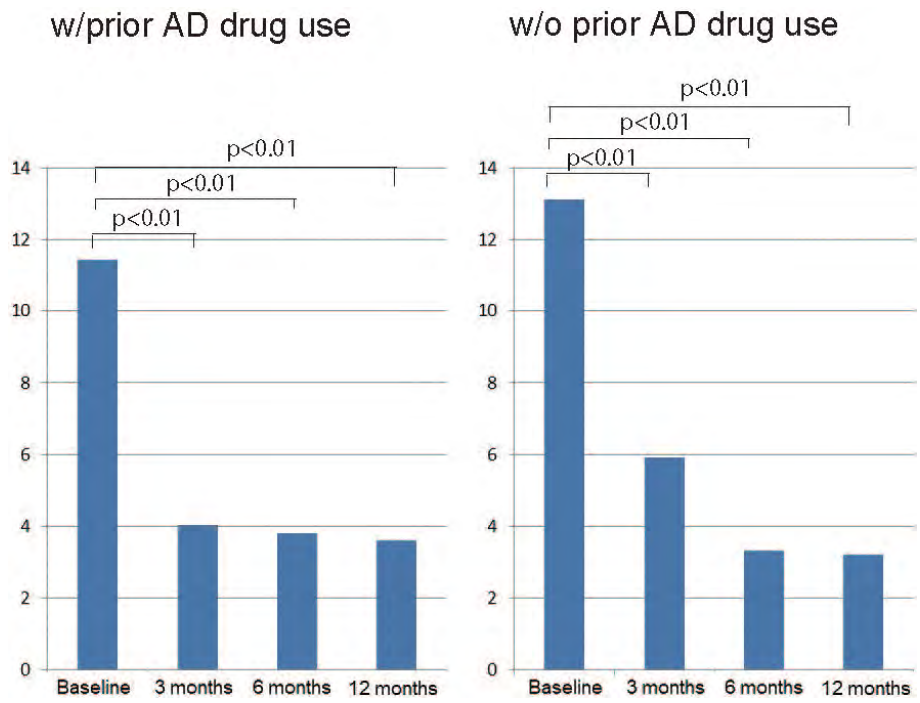

Figure 3 Changes in NPI scores in patients with or without prior AD drug use

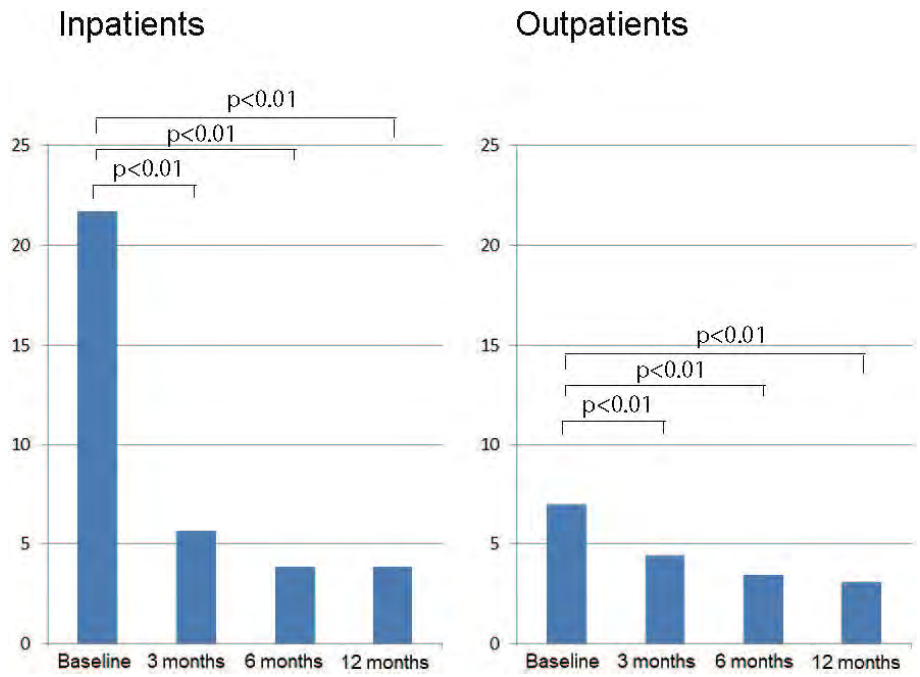

Figure 4 Changes in NPI scores in inpatients and outpatients

(CP equivalent, 113.0 mg) after 12 months of treatment, which included aripiprazole (53%) and quetiapine (47%) (Table 3; Figures 5, 6).

Discussion

In this 12-month follow-up, pharmacotherapy was assessed in a Japanese clinical practice setting for its effectiveness and safety in patients presenting with BPSD, which are particularly associated with AD, of all forms of dementia. Given that the focus of this study was on validating its indications in a broad Japanese AD population in a routine clinical practice setting, but not in a narrow population of patients with AD such as those enrolled in clinical

Table 3 Inpatients and outpatients on antipsychotics and combination therapy at baseline, 3, 6 and 12 months and transition of patients from inpatient to outpatient antipsychotic treatment

	No. of patients on antipsychotics	Baseline	3 months	6 months	12 months
Inpatients (n = 36)	On an inpatient basis	27	17	12	8
	On an outpatient basis	0	10	6	4
Outpatients (n = 66)	On an inpatient basis	0	0	0	0
	On an outpatient basis	13	13	10	10
Total number of patients on antipsychotics	On an inpatient basis	27	17	12	8
	On an outpatient basis	13	23	16	14
Proportion of patients on combination therapy (%)	On an inpatient basis	75.0	94.4	80.0	61.5
	On an outpatient basis	19.7	30.7	25.0	25.5

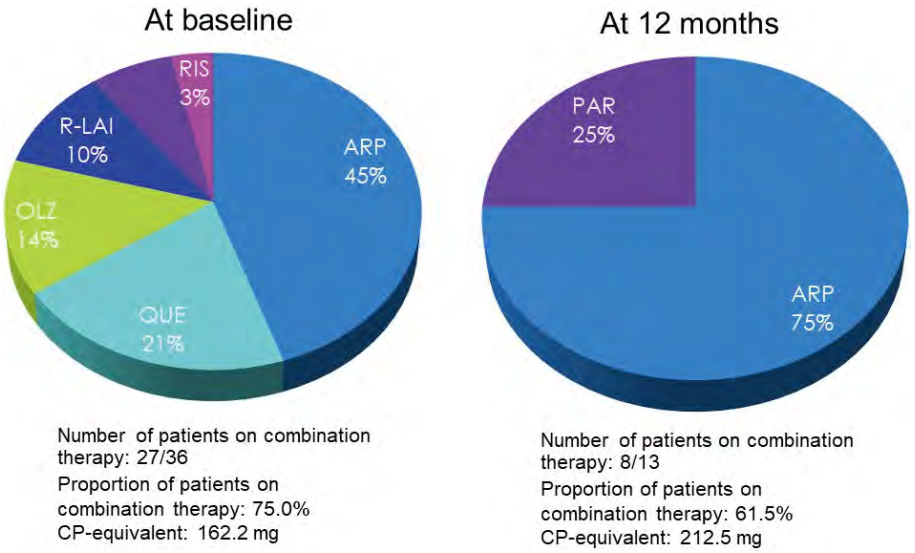

Figure 5 Proportion of inpatients on combination therapy with antipsychotics

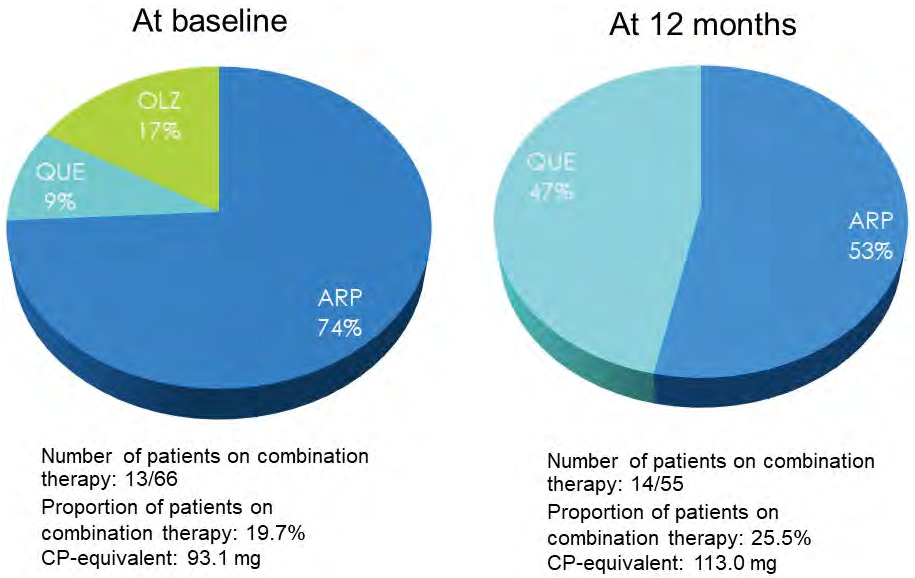

Figure 6 Proportion of outpatients on combination therapy with antipsychotics

trials, patients were deemed eligible for enrollment if they newly initiated treatment with an AChEI and an antipsychotic agent, and all patients with AD available for 12-month follow-up (n = 102) comprised the subjects in this study.

As regards its effects on cognitive function, anti-AD therapy often results in an initial moderate improvement followed by a gradual decrease thereafter in cognitive function. By the same token, the AD patients in this study showed a moderate improvement in MMSE scores but this improvement was not statistically significantly different from baseline. Again, given that a short-term study such as this should be more focused on the effect of anti-AD therapy on BPSD (primary outcome measure) and its tolerability than on its effects on cognitive function, the subsequent discussion will be focused on its effects on BPSD and its tolerability.

The NPI scores as a measure of BPSD were shown to improve markedly in patients initiating pharmacotherapy in this study. While this may be accounted for in part by the fact that all patients were initially admitted to accommodate their respective condition, here, detailed attention will be devoted to other potential contributing factors.

The improvement in NPI scores varied widely depending on two patient-related factors. First, this had to do with the presence or absence of prior AD drug use. In this study, the improvement in NPI scores was shown to be significant in all patients, irrespective of prior AD drug use, but even more so in those with no prior AD drug use (Figure 3). This was thought likely to be due in large part to the differences in NCI severity at baseline between the patients. Indeed, the NPI scores were shown to be 13.13 at baseline and therefore of much greater severity in those newly initiating the study treatment (i.e., an AChEI plus or minus an antipsychotic agent) compared to 11.45 in those switching to the study treatment from any other AD drug (those with prior AD drug use). This large difference noted at baseline diminished after 3, 6 and 12 months of treatment (5.91/4.03, 3.3/3.8, and 3.2/3.7, respectively, among those with no prior AD drug use/those with prior AD drug use). The greater improvement in NPI scores in the no prior AD drug use group seem to be due to severer disease at baseline. However, despite this large difference in NPI scores at baseline, the MMSE scores at baseline were not significantly different between those newly initiating the study treatment and those switching to the study treatment at 18.55 and 16.32, respectively, suggesting that the severity of BPSD as assessed by NPI scores was not necessarily concurrent or consistent with the decline of cognitive function.

Another background factor thought likely to have affected the changes in NPI scores was the difference in patient status as inpatients and outpatients. As in those newly initiating the study treatment and those switching to the study treatment from previous therapy, the NPI scores differed widely between the inpatients and outpatients, with this difference being even larger than that between those newly initiating the study treatment and those switching to the study treatment from previous therapy. Again, the NPI scores were shown to be 21.72 at baseline and therefore of much greater severity in inpatients than in outpatients (7.00), while this large difference noted at baseline diminished after 3, 6 and 12 months of treatment (5.63/4.43, 3.88/3.44 and 3.86/3.10, respectively, among inpatients/outpatients). This is in complete agreement with the observation in our clinical practice that in most cases, AD patients are newly admitted to our hospital at the request of their caregivers (families) who have had difficulty managing their BPSD. However, despite this large difference in NPI scores at baseline, the MMSE scores at baseline were not significantly different between inpatients and outpatients at 17.93 and 16.97, respectively, thus confirming that the severity of BPSD as assessed by NPI scores was not concurrent or consistent with the decline of cognitive function.

Apart from this, the significant improvement in NPI scores achieved with the study treatment may also be accounted for pharmacologically. The NPI scores improved remarkably in inpatients and those newly initiating pharmacotherapy; due to their greater NPI severity at baseline, however, these patients tended to receive antipsychotics and/or mood stabilizers concurrently with the AChEI (27/36 inpatients and 20/45 patients newly initiating treatment). Furthermore, given that, of the 10 behavioral domains in NPI, “delusions” and “aberrant motor behavior” were significantly improved from baseline in these patients, the

marked improvement in NPI scores could be accounted for in large part by the effects of concurrent antipsychotics and/or mood stabilizers among these patients.

In contrast, the NPI scores significantly improved in those switching to the study treatment (i.e., those with prior AD drug use) who had been shown to be of lesser NPI severity at baseline ($P < 0.05$, paired t-test) and tended to improve in outpatients newly initiating treatment who had also been shown to be of lesser NPI severity at baseline (mean NPI score, 7.00). Of note, only 20 of the 58 patients switching to the study treatment and 13 of the 66 patients newly initiating treatment had been receiving antipsychotics and/or mood stabilizers, respectively. Thus, it was thought unlikely that the marked improvement in their NPI scores were due to these concurrent medications and quite likely that the improvement in their NPI scores was primarily due to the effect of the AChEI in improving BPSD.

As for evidence for antipsychotic efficacy, the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) were conducted in 421 AD patients who presented with psychotic symptoms (e.g., delusions and hallucinations), aggression and irritability to evaluate the efficacy of atypical antipsychotics (i.e., olanzapine, quetiapine, risperidone) versus placebo, demonstrating that the atypical antipsychotics were not superior to placebo and offered no benefit over placebo, given their adverse effects[3]. On the other hand, Yunusa et al. conducted a network meta-analysis in 2019 of clinical trials conducted to date[8] to evaluate the relative benefits and safety of atypical antipsychotics in the treatment of BPSD, and demonstrated the efficacy of atypical antipsychotics (aripiprazole, quetiapine, and risperidone) on BPSD. By the same token, this study provided enough evidence for the effectiveness of atypical antipsychotics in AD patients with BPSD, given that the study treatment led to a significant improvement in their NPI scores and significantly improved "delusions" and "aberrant motor behavior", of the behavioral domains in NPI, among the study subjects.

After the FDA warning[4], the J-CATIA study was performed in Japan, in which 10,079 Japanese patients with AD were followed up for 24 weeks[9]. In this study, 71.4% were taking atypical antipsychotics (quetiapine, risperidone, olanzapine, aripiprazole, and others) and others were taking typical antipsychotics (tiapride, sulpiride, and levomepromazine). Arai et al. reported that patients with AD for whom antipsychotic treatment was started during the follow up period had increased mortality. The daily chlorpromazine equivalent doses were not higher in the patients who died than the whole exposed group[9].

Though there are indications that antipsychotic agents are associated with the risk of increasing mortality, they exert certain effects on selected BPSP (e.g., hallucinations, delusions, and agitation) and therefore cannot be dispensed with in real-world clinical settings. Thus, the authors conclude that while antipsychotics may be used, as the need arises, in AD patients whose BPSD are so severe as to require inpatient care, attention should be focused on reducing their dose or discontinuing them as their symptoms become alleviated, as well as on using antipsychotics with full understanding of their characteristics and each patient's symptoms and integrating them nicely with non-pharmacological therapy.

This study has some limitations. First, it included only an insufficient number of AD patients. Second, it was conducted as a retrospective study with no comparative control group. Third, BPSD were not evaluated in those with any other form of dementia than AD. Given the paucity of clinical evidence in Japan for the effectiveness of antipsychotic agents against BPSD, however, this study may represent a valuable addition to the literature, in that it corroborated the earlier findings reported overseas on their efficacy against BPSD.

Conclusions

The authors followed up the medical charts of AD patients newly initiating pharmacotherapy with the anti-AD agent galantamine and concurrent antipsychotic agents in Japanese AD patients with BPSD, evaluated a total of 102 patients who were available for 12-month follow-up, and confirmed the effectiveness and safety of the study treatment for up to 12 months. While how best to incorporate antipsychotics into the treatment of BPSD in clinical settings lies in the hands of us Japanese clinicians, accumulation of further clinical evidence is

eagerly awaited in the years to come.

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Author contributions

MF and TI both contributed equally to the design and conduct of the study. MF performed the statistical analysis of the study data and TI oversaw the statistical analysis and interpretation of the study data. MF wrote and revised the manuscript and TI participated in the writing and revision of the manuscript. The authors have read and approved the manuscript for publication.

Conflicts of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Original Articles

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Introduction of a Multidisciplinary Preoperative Clinic at Juntendo University Hospital - A Retrospective Observational Study Focusing on Effects of Preoperative Interventions on Clinical Outcomes

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Objectives: To investigate the effects of interventions provided by a multidisciplinary team consisting of anesthesiologists, dentists, pharmacists, and nurses at a Preoperative Clinic (POC) on postoperative outcomes.
Methods: We retrospectively investigated patients who underwent preoperative evaluation at the POC at Juntendo University Hospital between May and July, 2019. Patients were divided into intervention and non-intervention groups according to whether they received intervention(s) at the POC or not. Postoperative outcomes were compared between the groups, before and after propensity score (PS) matching.
Results: We investigated 909 patients who completed POC evaluation and underwent surgery. Patients in the intervention group (n = 455 [50.1%]) received at least one intervention delivered, in the order of higher delivery frequencies, by dentists, pharmacists, nurses, and anesthesiologists. Before PS matching, the intervention group was associated with older age, more frequent cardiovascular comorbidities, and higher ASA-PS grades than the non-intervention group, while neither frequencies nor severities of postoperative complications differed between the groups. These outcomes did not differ between 382 PS-matched pairs with comparable risk factors either.
Conclusions: Before PS matching, postoperative outcomes did not differ between the groups, although the intervention group was associated with higher risks. These suggested that POC interventions could have improved postoperative outcomes in the higher-risk intervention group to the same level as in the non-intervention group. However, such potential beneficial effects of interventions could not be proven after PS matching. Further studies are required to elucidate effects of POC interventions on postoperative outcomes.

Key words: postoperative complication, preoperative clinic, preoperative evaluation, preoperative management

Introduction

Robust preoperative assessment and appropriate management of surgical patients by anesthesiologists are essential to optimize postoperative outcomes[1)]. Nonetheless, preoperative assessment by anesthesiologists has conventionally been carried out during a limited time after patients' hospitalization[2)]. As such an approach may result in suboptimal outcomes, preoperative patient management at an outpatient-based preoperative clinic (POC) has been increasing[3)]. Currently, however, there is no

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standardized structure or guideline for a POC system.

Organizational designs of the POC can roughly be divided into single-professional and multi-professional models[4]. Various studies regarding single-professional models have been reported[5-11]. However, studies of multi-professional models remain limited, and the benefits of preoperative evaluation provided by multi-professional POC teams remain to be clarified.

This study aimed to introduce a multidisciplinary POC team at our institute, consisting of anesthesiologists, dentists or dental hygienists, pharmacists, and nurses, and to assess the impact of interventions provided by the POC team on clinical outcomes.

Materials and Methods

The Research Ethics Committee at Juntendo University Hospital (JUH) approved this study (No. H19-0157, September 20th, 2019) with a waiver of informed consent. This study investigated a single-center historical cohort of patients who visited the POC and underwent surgery at JUH, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[12].

Conceptual framework of the POC at JUH

Approximately 10,000 surgeries under anesthesia managed by anesthesiologists are performed annually at JUH. Since the establishment of the POC in 2019, preoperative assessment and evaluation of non-obstetric patients scheduled for elective surgery have been carried out at the POC. The POC is managed by a collaborative team consisting of above-mentioned four disciplines. In principle, a patient has interviews and/or consultations with a pharmacist, dentist or dental hygienist, anesthesiologist, and nurse in this order. While the order may vary depending on provider availability, an interview with a pharmacist and oral screening by a dental staff are completed before a consultation with an anesthesiologist, as the anesthesiologist requires relevant information on medication and oral health for anesthetic planning. An interview with a nurse is typically performed last as it also involves confirmation of written informed consent.

One of the primary roles of pharmacists is to manage patients' medication, such as anti-coagulants, in preparation for surgery. The dental staff perform oral health screening, and clearly indicate the condition of each tooth by color/shape-coding in the medical record. This practice enables anesthesiologists and nurses in the operating room to recognize any tooth requiring caution during intubation and to compare pre- and post-operative oral conditions. The roles of the anesthesiologists at the POC, such as evaluating preoperative health conditions and providing information on anesthesia, remain unchanged from those previously performed after patients' hospitalization. However, the POC provides opportunities for patients to receive information on anesthesia in advance to have sufficient time, allowing for better degrees of comprehension of, and self-preparation for, scheduled procedures. To promote patient comprehension further, patients are encouraged to watch original movies showing typical anesthesia procedures for scheduled surgery during their waiting time. Nurses' roles include arranging patients' orders, explaining an in-hospital perioperative flow of care, assessing physical conditions such as skin and joint health, confirming completion of required documentations, and informing a relevant section staff of patient information. Having nurses be the final discipline to interact with patients also allows patients to ask any open questions. Information on preoperative evaluation is shared among the multidisciplinary team using check sheets and POC medical records.

Preoperative interventions in this study refer to any intervention delivered by any POC discipline. These may include anesthesiologists ordering additional examinations based on their POC assessment, dentists/dental hygienists ordering oral treatment from the Department of Oral and Maxillofacial Surgery, and any involved disciplines consulting with specialists for expert advice. Among diverse roles of nurses, however, nurse-delivered interventions in this study were limited to interactions with other disciplines/sections, considering eligible quantitative data collection. Interventions are performed when each profession deemed them necessary. However, necessary interventions are not always performed, since some patients are unwilling to receive them, e.g. because of the extra time and/or expense required to perform them. In addition, a decision as to whether or not a certain intervention is necessary for a certain health condition can vary among individuals in each profession because there

are not always strict criteria for interventions to be performed by the profession. Therefore, in the present study, it was highly likely that not all patients in the non-intervention group did not need interventions, and conversely, not all patients in the intervention group needed interventions.

Patient inclusion and data collection

Included were patients scheduled for elective surgery other than cardiovascular surgery and obstetric surgery, who visited the POC at JUH between May 7th and July 31st, 2019. Patients scheduled for obstetric surgery were not included because their preoperative conditions are specifically evaluated by our obstetric anesthesia team. Further, patients scheduled for cardiovascular surgery were not included because initially, they did not visit the POC during the study period, although currently, they visit the POC. Excluded were patients whose data were insufficient and those whose surgeries were canceled subsequently. Patients' demographic, anesthetic, and surgical data were collected, including age, sex, clinical departments, comorbidities, American Society of Anesthesiologists physical status (ASA-PS), surgical procedures, and methods of anesthesia. Data on POC intervention(s) were collected from POC medical records. Patients receiving any intervention and those receiving no intervention were grouped into, and defined as, the intervention group and the non-intervention group, respectively (Figure 1).

Postoperative complications included hospital mortality, reoperations, and any deviation from the natural postoperative course[13], including postoperative nausea and vomiting (PONV), delirium, any intubation-related airway injuries, and any organ dysfunction categorized into defined body parts[14]. Severities of postoperative complications ranked by the Clavien-Dindo classification (CDC)[13] were also explored. While the CDC is typically classified into grades from I to V, we included patients without any complications as Grade 0. Further, we combined grades IVa and IVb into Grade IV because of difficult discrimination between single and multiple organ dysfunction(s). Information on the type and severity of postoperative complications was collected from the discharge summary as well as from other postoperative records in the electronic medical record.

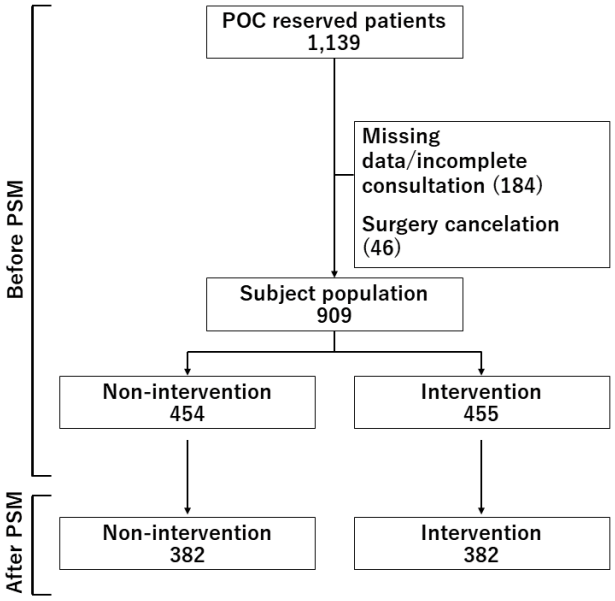

Figure 1 Flow chart outlining the inclusion and exclusion criteria of this study
POC: Outpatient-based Preoperative Clinic
PSM: Propensity score matching

Statistical analysis

Continuous variables are summarized as Median [Interquartile Range]. Categorical variables are summarized as Number (Percentage). Data were compared between groups with the Mann-Whitney *U* test, Fisher's exact test, or the chi-square test. First, clinical backgrounds and postoperative outcomes were compared between intervention and non-intervention groups in the total cohort. Then, these were compared after the nearest neighbor propensity score (PS) matching in 1:1 ratio with a 0.05 caliper was applied to create PS-matched pairs of patients by adjusting differences in age, sex, clinical departments, surgical procedures, anesthesia methods, and ASA-PS grades, as reported in a previous study investigating the effect, on postoperative mortality, of a single-profession POC involving an intervention to encourage high-risk patients to visit the POC[6]. To compare clinical backgrounds between the groups, a p value < 0.05 was considered statistically significant. Meanwhile, to compare two major endpoints, including frequencies of complications and severities of complications (ranked by CDC grades), a p value < 0.025 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics

27.0.1.0. (IBM Corp., Armonk, NY, USA).

Results

Clinical backgrounds

During the study period, 1,139 patients who met the inclusion criteria visited the POC at JUH. After excluding 184 patients whose data were insufficient and 46 patients whose surgeries were canceled subsequently, 909 patients were included in the study (Figure 1). Among them, 455 patients (50.1%) and 454 patients (49.9%) were grouped into intervention and non-intervention groups, respectively (Figure 1, Table 1). Compared to the non-intervention group, the intervention group included higher proportions of the elderly (≥ 65 years; 211/455 [46.4%] *vs.* 148/454 [32.6%], $p < 0.0001$), females, patients with hypertension, patients with cardiovascular disease, and/or patients classed as ASA-PS grades ≥ 2 (338/455 [74.3%] *vs.* 283/454 [62.3%], $p = 0.0001$) (Table 1).

Interventions provided in the intervention group before PS matching

In 455 patients in the intervention group, interventions were delivered, in the order of higher delivery frequencies, by dentists/dental hygienists ($n = 334$ [73.4% of the intervention group]), pharmacists ($n = 116$ [25.5%]), nurses ($n = 66$ [14.5%]), and anesthesiologists ($n = 59$ [13.0%]) (Table 2).

Following dental screening at the POC, 334 patients (73.4%) received care for any oral problems, especially for fragile teeth, at the Department of Oral and Maxillofacial Surgery, such as mouth guard preparation ($n = 190$ [41.8%]) and/or oral cleaning ($n = 139$ [30.5%]) (Table 2).

Pharmacists performed interventions in 116 patients (25.5%). Pharmacists instructed 90 patients (19.8%) to withhold or continue medications, such as complementary and alternative medicines (CAMs), including supplements and Chinese herbal medicines ($n = 71$ [15.6%]), and anti-coagulants ($n = 11$ [2.4%]) (Tables 2). In addition, pharmacists consulted with specialists for 39 patients (8.6%), e.g. regarding perioperative management of anti-coagulants ($n = 15$ [3.3%]) (Table 2).

Nurses performed interventions, which were limited in this study to interactions with other disciplines/sections, in 66 patients (14.5%), including informing other health care providers of patients' critical information (Table 2).

Anesthesiologists performed interventions in 59 patients (13.0%), including ordering additional examinations ($n = 41$ [9.0%]) and/or consulting with specialists for expert advice ($n = 20$ [4.4%]) (Table 2).

Clinical outcomes

Neither frequencies of postoperative complications nor CDC grades indicating their severities differed between intervention and non-intervention groups (Table 3). Frequencies of intubation-related complications, mostly sore throats and/or hoarseness, did not differ between the two groups. No tooth injury occurred in either group.

By applying PS matching, 382 pairs of patients with comparable clinical backgrounds were created from both groups (Tables 1 & 3). Neither frequencies of postoperative complications nor CDC grades differed between the PS-matched groups (Table 3).

Discussion

Nearly half of preoperative patients visiting the multidisciplinary POC received at least one intervention. Interventions were delivered, in the order of higher delivery frequencies, by dentists/dental hygienists, pharmacists, nurses, and anesthesiologists. Initially, we intended to compare postoperative outcomes between patients who underwent surgery before and after the establishment of the POC to examine effects of the POC on outcomes, similar to our previous study investigating the effect of the POC system on the surgery cancellation rate[15]. However, such a study design cannot be free from a time-dependent bias resulting from comparing data collected in entirely different study periods. Further, what could improve outcomes was considered to be any intervention(s) provided at a POC, and not the patient's POC visit itself. Therefore, we investigated patients who visited the POC over the same period of time, and compared postoperative outcomes between patients who received any intervention(s) at the POC and those who did not, to explore effects of the POC intervention(s) on outcomes.

Roles of the POC

The roles of a multidisciplinary POC include early assessments of patients' preoperative condi-

Table 1 Patients' demographics, surgical, and anesthetic characteristics in the total cohort, intervention group, and non-intervention group before and after propensity score (PS) matching

	Before PS matching				After PS matching			
	Total cohort *n* = 909	Intervention *n* = 455	Non-intervention *n* = 454	*p* value	Total cohort *n* = 764	Intervention *n* = 382	Non-intervention *n* = 382	*p* value
Age	58 [41-71]	63 [47-72]	52 [34-70]	<.0001	58 [44-71]	60.5 [45-71]	56 [41-71]	0.1530
Gender, females	475 (52.3)	255 (56.0)	220 (48.5)	0.0240	393 (51.4)	204 (53.4)	189 (49.5)	0.3109
Comorbidities[a)]	428 (47.1)	229 (50.3)	199 (43.8)	0.0540	370 (48.4)	183 (47.9)	187 (49.0)	0.8281
Hypertension	261 (28.7)	146 (32.1)	115 (25.3)	0.0278	223 (29.2)	113 (29.6)	110 (28.8)	0.8736
Respiratory	149 (16.4)	70 (15.4)	79 (17.4)	0.4214	138 (18.1)	67 (17.5)	71 (18.6)	0.7779
Cardiovascular	104 (11.4)	65 (14.3)	39 (8.6)	0.0089	77 (10.1)	39 (10.2)	38 (9.9)	1.0000
Diabetes mellitus	97 (10.7)	49 (10.8)	48 (10.6)	1.0000	82 (10.7)	38 (9.9)	44 (11.5)	0.5592
Neurological	53 (5.8)	32 (7.0)	21 (4.6)	0.1564	44 (5.8)	23 (6.0)	21 (5.5)	0.8768
ASA-PS								
1	288 (31.7)	117 (25.7)	171 (37.7)	0.0004	231 (30.2)	111 (29.1)	120 (31.4)	0.7641
2	566 (62.3)	305 (67.0)	261 (57.5)		487 (63.7)	247 (64.7)	240 (62.8)	
3	55 (6.1)	33 (7.3)	22 (4.8)		46 (6.0)	24 (6.3)	22 (5.8)	
Clinical departments				0.0003				0.2170
Orthopedic	262 (28.8)	144 (31.6)	118 (26.0)		220 (28.8)	115 (30.1)	105 (27.5)	
Urological	110 (12.1)	41 (9.0)	69 (15.2)		106 (13.9)	40 (10.5)	66 (17.3)	
Breast Oncologic	103 (11.3)	63 (13.8)	40 (8.8)		87 (11.4)	48 (12.6)	39 (10.2)	
Colorectal	72 (7.9)	38 (8.4)	34 (7.5)		58 (7.6)	29 (7.6)	29 (7.6)	
Esophageal & Gastric	63 (6.9)	34 (7.5)	29 (6.4)		50 (6.5)	30 (7.9)	20 (5.2)	
Pediatric	62 (6.8)	14 (3.1)	48 (10.6)		34 (4.5)	14 (3.7)	20 (5.2)	
Plastic & Reconstructive	61 (6.7)	29 (6.4)	32 (7.0)		51 (6.7)	24 (6.3)	27 (7.1)	
General Thoracic	50 (5.5)	27 (5.9)	23 (5.1)		47 (6.2)	26 (6.8)	21 (5.5)	
Hepatobiliary & Pancreatic	40 (4.4)	19 (4.2)	21 (4.6)		34 (4.5)	15 (3.9)	19 (5.0)	
Otorhinolaryngological	38 (4.2)	18 (4.0)	20 (4.4)		38 (5.0)	18 (4.7)	20 (5.2)	
Gynecological	25 (2.8)	13 (2.9)	12 (2.6)		19 (2.5)	11 (2.9)	8 (2.1)	
Neurosurgical	12 (1.3)	6 (1.3)	6 (1.3)		10 (1.3)	4 (1.0)	6 (1.6)	
Dermatological	3 (0.3)	2 (0.4)	1 (0.2)		1 (0.3)	1 (0.3)	1 (0.2)	
Ophthalmological	3 (0.3)	3 (0.7)	0 (0)		3 (0.3)	3 (0.8)	0 (0)	
Internal Medical	5 (0.5)	4 (0.9)	1 (0.2)		5 (0.7)	4 (1.0)	1 (0.3)	
Surgical procedures				0.2078				0.9021
Open	685 (75.4)	355 (78.0)	330 (72.7)		573 (75.0)	289 (75.7)	284 (74.3)	
Laparoscopic	187 (20.6)	81 (17.8)	106 (23.3)		154 (20.2)	74 (19.4)	80 (20.9)	
Endoscopic	21 (2.3)	10 (2.2)	11 (2.4)		21 (2.7)	10 (2.6)	11 (2.9)	
Robot-assisted	16 (1.8)	9 (2.0)	7 (1.5)		16 (2.1)	9 (2.4)	7 (1.8)	
Anesthesia methods				0.2042				1.0000
General anesthesia	886 (97.5)	440 (96.7)	446 (98.2)		749 (98.0)	374 (97.9)	375 (98.2)	
Other	23 (2.5)	15 (3.3)	8 (1.8)		15 (2.0)	8 (2.1)	7 (1.8)	
Regional anesthesia				0.6747				0.4850
None	486 (53.5)	238 (52.3)	248 (54.6)		425 (55.6)	206 (53.9)	219 (57.3)	
Epidural anesthesia	202 (22.2)	98 (21.5)	104 (22.9)		165 (21.6)	84 (22.0)	81 (21.2)	
Nerve blocks	126 (13.9)	71 (15.6)	55 (12.1)		96 (12.6)	56 (14.7)	40 (10.5)	
Spinal anesthesia	26 (2.9)	15 (3.3)	11 (2.4)		20 (2.6)	11 (2.9)	9 (2.4)	
Spinal-epidural	2 (0.2)	1 (0.2)	1 (0.2)		2 (0.3)	1 (0.3)	1 (0.3)	
Other	67 (7.4)	32 (7.0)	35 (7.7)		56 (7.3)	24 (6.3)	32 (8.4)	

Data are shown as Median [Interquartile Range] or Number (Percentage). Continuous variables were compared between Groups with the Mann-Whitney *U* test. Categorical variables were compared with the chi-square test or Fisher's exact test.

a) Some patients had multiple comorbidities.

ASA-PS, American Society of Anesthesiologists physical status.

Table 2 Numbers of preoperative interventions provided by multi-professions at the preoperative clinic (POC) in the intervention group before and after propensity score (PS) matching

Providers and interventions	Before PS matching (n = 455)	After PS matching (n = 382)
Dentists/Dental hygienists	**334 (73.4)**	**288 (75.4)**
Mouth guard preparation	190 (41.8)	159 (41.6)
Oral cleaning	139 (30.5)	130 (34.0)
Other	29 (6.4)	23 (7.6)
Pharmacists	**116 (25.5)**	**94 (24.6)**
Medication instructions	**90 (19.8)**	**74 (19.4)**
CAM	71 (15.6)	59 (18.1)
Anti-coagulant	11 (2.4)	7 (1.8)
Anti-rheumatic agent	8 (1.8)	1 (0.3)
Hormonal agent	2 (0.4)	2 (0.5)
Hypoglycemic agent	1 (0.2)	1 (0.3)
Anti-hypertensive agent	1 (0.2)	1 (0.3)
Other	3 (0.7)	3 (0.8)
Consultations with specialists	**39 (8.6)**	**29 (7.6)**
CAM	3 (0.7)	3 (0.8)
Anti-coagulant	15 (3.3)	9 (2.4)
Anti-rheumatic agent	8 (1.8)	6 (1.6)
Hormonal agents	3 (0.7)	3 (0.8)
Hypoglycemic agent	1 (0.2)	1 (0.3)
Anti-hypertensive agent	0 (0.0)	0 (0.0)
Other	9 (2.0)	7 (1.8)
Nurses	**66 (14.5)**	**49 (12.8)**
Interactions with others	**66 (14.5)**	**49 (12.8)**
Anesthesiologists	**59 (13.0)**	**43 (11.3)**
Consultations with specialists	**20 (4.4)**	**16 (4.2)**
Additional examinations	**41 (9.0)**	**29 (7.6)**
Venous ultrasound	15 (3.3)	10 (2.6)
Blood chemistry test (CMP)	6 (1.3)	6 (1.6)
Echocardiography	6 (1.3)	2 (0.5)
Blood coagulation test	3 (0.7)	2 (0.5)
D-dimer test	3 (0.7)	2 (0.5)
X-ray	3 (0.7)	2 (0.5)
Electrocardiogram	2 (0.4)	1 (0.3)
Pulmonary function test	1 (0.2)	1 (0.3)
Other	4 (0.9)	4 (1.0)

Data are shown as Number (Percentage).
Some patients received multiple interventions.
CAM, complementary and alternative medicine; CMP, comprehensive metabolic panel.

Table 3 Frequencies of postoperative complications and their severities according to Clavien-Dindo Classification (CDC) in the total cohort, intervention group, and non-intervention group before and after propensity score (PS) matching

	Before PS matching				After PS matching			
	Total cohort (n = 909)	Intervention (n = 455)	Non-intervention (n = 454)	p value	Total cohort (n = 764)	Intervention (n = 382)	Non-intervention (n = 382)	p value
Complications[a)]	272 (29.9)	143 (31.4)	129 (28.4)	0.3465	224 (29.3)	111 (29.1)	113 (29.6)	0.9367
Death	2 (0.2)	1 (0.2)	1 (0.2)	1.0000	1 (0.1)	0 (0.0)	1 (0.3)	1.0000
Reoperation	12 (1.3)	4 (0.9)	8 (1.8)	0.2634	8 (1.0)	2 (0.5)	6 (1.6)	0.2865
PONV	69 (7.6)	35 (7.7)	34 (7.5)	1.0000	55 (7.2)	30 (7.9)	25 (6.5)	0.5759
Intubation-related	55 (6.1)	26 (5.7)	29 (6.4)	0.6793	48 (6.3)	24 (6.3)	24 (6.3)	1.0000
Sore throat/hoarseness	50 (5.5)	24 (5.3)	26 (5.7)		43 (5.6)	22 (5.8)	22 (5.8)	
Lip injury	4 (0.4)	1 (0.2)	3 (0.7)		3 (0.4)	0 (0.0)	3 (0.8)	
Vocal cord paralysis	1 (0.1)	1 (0.2)	0 (0.0)		1 (0.1)	1 (0.3)	0 (0.0)	
Tooth injury	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Respiratory	37 (4.1)	22 (4.8)	15 (3.3)	0.3139	31 (4.1)	19 (5.0)	12 (3.1)	0.2711
Gastric	35 (3.9)	16 (3.5)	19 (4.2)	0.6105	31 (4.1)	14 (3.7)	17 (4.5)	0.7144
Cardiac	34 (3.7)	20 (4.4)	14 (3.1)	0.3824	27 (3.5)	13 (3.4)	14 (3.7)	1.0000
Infections	33 (3.6)	20 (4.4)	13 (2.9)	0.2873	26 (3.4)	15 (3.9)	11 (2.9)	0.5503
Delirium	28 (3.1)	19 (4.2)	9 (2.0)	0.0823	22 (2.9)	13 (3.4)	9 (2.4)	0.5173
Deep vein thrombosis	8 (0.9)	7 (1.5)	1 (0.2)	0.0691	3 (0.4)	2 (0.5)	1 (0.3)	1.0000
Other	90 (9.9)	45 (9.9)	45 (9.9)	1.0000	71 (9.3)	30 (7.9)	41 (10.7)	0.2125
CDC grade[b)]				0.2056				0.2035
0	637 (70.1)	312 (68.6)	325 (71.6)		540 (70.7)	271 (70.9)	269 (70.4)	
I	157 (17.3)	78 (17.1)	79 (17.4)		130 (17.0)	62 (16.2)	68 (17.8)	
II	84 (9.2)	49 (10.8)	35 (7.7)		69 (9.0)	37 (9.7)	32 (8.4)	
IIIa	15 (1.7)	11 (2.4)	4 (0.9)		14 (1.8)	10 (2.6)	4 (1.0)	
IIIb	10 (1.1)	3 (0.7)	7 (1.5)		7 (0.9)	2 (0.5)	5 (1.3)	
IV	4 (0.4)	1 (0.2)	3 (0.7)		3 (0.4)	0 (0.0)	3 (0.8)	
V	2 (0.2)	1 (0.2)	1 (0.2)		1 (0.1)	0 (0.0)	1 (0.3)	

Data are shown as Number (Percentage). Groups were compared with the chi-square test or Fisher's exact test.
a) Some patients developed multiple complications.
b) CDC grades, including CDC grade 0 indicating no complication, were compared between the groups.
PONV, postoperative nausea and vomiting.

tions allowing for early recognition of needs for additional examinations and specialty consultations, optimization of airway conditions to prevent airway injuries and postoperative infections, optimization of medication management, and enhancement of close, mutual communications among medical providers, patients, and their families[1, 16]. ASA practice advisories suggest POC benefits from a variety of interventions[17]. However, only a few studies report beneficial effects of the POC on clinical outcomes, mostly by exploring impacts of interventions provided by a single profession alone[5–11].

Roles of dentists and dental hygienists

In this study, although the dental staff provided interventions in 73.4% of patients receiving POC intervention(s), frequencies of postoperative infections did not differ between the groups. Because our study included various surgical procedures, we could not detect beneficial effects of oral care on postoperative infections possibly by overlooking such effects in patients undergoing high-risk surgery.

In this study, however, frequencies of airway injury did not differ between intervention and non-intervention groups, and further, tooth injuries occurred in neither group. These results suggested that preoperative dental interventions, such as

mouth guard preparation and/or oral cleaning, could have, at least, reduced frequencies of tooth injuries in patients in the intervention group with fragile teeth and/or poor oral hygienic conditions to a comparable level seen in patients in the non-intervention group almost free from oral problems.

Roles of pharmacists

Pharmacists are more likely to prevent medication-associated errors at the POC than in the ward after hospitalization, through earlier and more comprehensive identification of patients' medication requiring appropriate perioperative guidance[18]. It should be noted that along with anti-coagulants, substantial numbers of CAMs taken by a number of patients require precautions for their perioperative uses[19].

Roles of nurses

Reportedly, roles of preoperative nursing care include preoperative screening and assessment, coordination, communication and collaboration, patient and family education, patient- and family-centered care, preoperative patient contact, and scheduling[20]. Our study explored 'collaboration' as an essential task to enhance preoperative management via close, mutual communications among nurses, other medical care providers, patients, and their families.

Roles of anesthesiologists

Major roles of anesthesiologists at our POC include evaluating patients' health condition as thoroughly as possible, ordering additional examinations depending on patients' comorbidities, and consulting with specialists for expert advice. Another essential role of anesthesiologists at our POC not included in this study is responding to consultations from attending physicians regarding how to manage perioperative care, including anesthesia, in patients with severe comorbidities.

Clinical outcomes

To date, studies regarding a role of the POC in reducing mortality are limited. Only one study by Blitz et al.[6], which compared 35,535 and 28,883 patients visiting and not visiting a POC, respectively, reported a small but statistically significant reduction in mortality in the visitors (0.06% *vs.* 0.08%). Given the low mortality rate, studies enrolling a large number of patients would be required to demonstrate mortality benefits.

Before PS matching in this study, the intervention group included higher proportions of the elderly, females, patients with hypertension, patients with cardiovascular disease, and/or patients classed as ASA-PS ≥ 2, compared with the non-intervention group. Therefore it could be expected that the intervention group would be associated with more frequent and severer postoperative complications. However, no significant inter-group difference was found in frequencies nor severities of postoperative complications. These results suggested that POC intervention(s) could have improved clinical outcomes in the intervention group in such a way that frequencies/severities of postoperative complications in higher-risk patients who required POC intervention(s) could have been reduced to a level comparable to those seen in lower-risk patients mostly not requiring a POC intervention. However, we could not detect such beneficial effects of POC interventions, as no significant difference was found in frequencies or severities of postoperative complications between the PS-matched groups with comparable risk factors. Inclusions of a relatively small number of patients and a wider variety of surgical procedures, compared with previous studies[6, 21-24], might have hindered this study from showing beneficial effects of POC interventions. However, the possibility could not be excluded that preoperative dental interventions delivered in 73.4% of patients in the intervention group could have prevented airway injuries, especially tooth injuries, and further, postoperative infections in patients with fragile teeth and/or poor oral hygienic conditions.

Study limitations

There were some limitations of this study. This study was a retrospective observational study conducted at a single institution including a relatively small number of patients. As this study included patients scheduled for various surgical procedures, different results might have been obtained from studies with different study designs, e.g. focusing on specific surgical procedures. A larger observational study involving more extended periods of time would be required to examine

whether POC interventions can exert any beneficial effects on clinical outcomes.

Conclusion

We introduced our POC consisting of a multidisciplinary team and examined its effects on clinical outcomes. We could not clearly demonstrate beneficial effects of interventions provided by the multidisciplinary POC team on postoperative outcomes, possibly because this retrospective observational study included a relatively small number of patients, multiple types of POC interventions, and various surgical procedures. However, the possibility could not be excluded that early interventions provided by the multidisciplinary POC team might exert some beneficial effect. The impact of POC interventions on clinical outcomes warrants further evaluation.

Data availability

The datasets related to this study are available from the corresponding author on reasonable request.

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Author contributions

YU, SI, and EI conceptualized this study. YU, SI, and OK collected data. YU, SI, SN, OK, and MH analyzed data. YU wrote the first draft of the manuscript. SI, GD, EI, and MH edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Original Articles

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Surgical Outcome after Sleeve Pneumonectomy for Thoracic Malignancy: A Comparison Between Salvage and Non-salvage

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Objectives: Tumors invading the tracheobronchial angle or carina have long presented a challenge due to the complexity of airway reconstruction and management; thus, few medical centers have developed experience with this type of surgery. In this report, we review our experience with Sleeve Pneumonectomy (SP) and analyze both operative risks and outcomes.

Materials and Methods: A retrospective review identified 34 patients who underwent SP: 19 underwent salvage SP and 15 underwent non-salvage SP. Salvage surgery was performed for recurrent lung cancer after chemoradiotherapy and could be considered if there were no other therapeutic options or in the presence of urgent symptoms, such as hemoptysis, obstructive pneumonia, superior vena cava syndrome, or tracheoesophageal fistula.

The perioperative morbidity and oncological outcomes of salvage and non-salvage SP were analyzed.

Results: Most cases were of lung cancer, whereas salvage SP included one case of SVC syndrome due to metastasis of colon cancer and one case of hemoptysis due to metastasis of leiomyosarcoma. Complications occurred in 47% of the non-salvage SP cases and 53% of the salvage SP cases. The 30-day mortality rates were zero in the non-salvage cases and 11% in the salvage cases. The 90-day mortality rates were 20% and 16% in the non-salvage and salvage groups, respectively.

Conclusions: The salvage of SP after chemoradiotherapy or in the presence of urgent symptoms is feasible. We believe that it can be an option that improves quality of life (QOL) through longer desease-free survival (DFS) and alleviation of symptoms, rather than waiting for tumor growth progression and exacerbation of symptoms.

Key words: lung cancer, sleeve pneumonectomy, carinal resection, tracheo-bronchial anastomosis

Introduction

Advancements in surgical and anesthetic techniques and postoperative management has enabled for the successful surgical resection of locally advanced lung cancers. In particular, tumors invading the tracheobronchial angle or carina have long presented challenges owing to the complexity of airway reconstruction and management. Moreover, sleeve pneumonectomy (SP) was performed in only 10 patients (9 with lung cancer and 1 with other tumors) according to the annual report of thoracic and cardiovascular surgeries in Japan in 2018[1]; thus, few medical centers have developed experience with this type of surgery. In this report, we review our experiences with SP and analyze both the operative risks and outcomes.

Material and methods

Study population

Between May 2008 to March 2023, 34 SP were performed at our institution for centrally located

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lung cancer and metastatic malignant tumors. A retrospective data review was performed on the surgical outcomes and clinicopathological characteristics under a waiver of informed consent approved by the Juntendo University School of Medicine Institutional Review Board, Tokyo, Japan (IRB approval number: 23-0118). No data were missing for any of the variables used in this study.

Indication, operative mode, and follow-up policy

When R0 was possible, PS was generally indicated for centrally located malignant tumors. Salvage surgery was performed for recurrent or persistent non-small cell lung cancer (NSCLC) after chemoradiotherapy (CRT) with curative intent in patients initially excluded from surgical resection. Surgery was considered if there were no other therapeutic options or in the presence of urgent symptoms, such as hemoptysis, obstructive pneumonia, superior vena cava (SVC) syndrome, or tracheoesophageal fistula. Patient selection is critical to obtain the positive benefits of a salvage surgery and careful re-staging should be performed before indicating a surgery as a salvage therapeutic option. Chest computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans are essential for restaging when a relapse or recurrent disease is suspected. All clinical cases required discussions at multidisciplinary lung cancer meetings. In this series, all operative approaches were essentially performed via open thoracotomy because of the technicality of the procedures. All patients underwent double-lumen endotracheal intubation. The surgical approach used was a standard posterolateral thoracotomy. No irreversible procedures were performed before thoracic cavity exploration and confirmation of resectability by frozen-section analysis. If required, en bloc resection of the tumor and adjacent structures (SVC, brachiocephalic vein, azygos vein, esophagus, phrenic nerve, vagus nerve, and left atrium) was performed. The recurrent laryngeal and vagus nerves were routinely identified and preserved, if possible. All tracheobronchial anastomoses were end-to-end anastomoses. A continuous running suture (4-5 stitches) was applied to the deepest site of the bronchial stump using 3-0 nonabsorbable monofilament sutures (Prolene, Ethicon Inc.). The remainder of the anastomosis was performed using an interrupted suture with 4-0 nonabsorbable monofilament sutures, called a hybrid anastomosis[2, 3]. Each suture was inserted through the full width of the bronchial wall, and all knots were tied outside of the lumen. The anastomosis was covered with a pericardial fat pad when needed, particularly in cases of severe diabetes mellitus, induction chemotherapy, or chemoradiotherapy. A chin stitch was frequently used to guide the trachea toward the periphery. When resection and reconstruction of the SVC were necessary, concomitant vascular reconstruction was performed with an expanded polytetrafluoroethylene (ePTFE) graft and 5-0 nonabsorbable monofilament sutures (Prolene, Ethicon Inc.). After pulmonary resection, a bronchoscopic examination was conducted on postoperative day 7 or before discharge. Routine bronchoscopic examinations were planned on postoperative days 14 and 28 and a grading sequence was used to describe bronchial healing[4].

Results

Table 1 summarizes the surgery types, clinicopathological features, and outcomes of the 34 patients who underwent SP. Nineteen patients underwent salvage surgery: no intraoperative mortalities were observed. Of the 34 cases, 32 were on the right side and approached by standard posterolateral thoracotomy. The majority of cases were lung cancer, whereas salvage SP included one case of SVC syndrome due to metastasis of colon cancer and one case of hemoptysis due to metastasis of leiomyosarcoma. In case 2, a left pneumonectomy was performed using standard posterolateral thoracotomy. Because the bronchial stump was diagnosed with a positive resection margin by intraoperative rapid pathological diagnosis, the patient was repositioned, the carina was resected with a median sternotomy, and the trachea and right main bronchus were anastomosed. In contrast, in case 12, left sleeve pneumonectomy was performed using standard posterolateral thoracotomy without median sternotomy. Case 1 was a 75 mm large cell neuroendocrine carcinoma to the right of segment 6. Pneumonectomy was performed because the tumor had spread to the right main bronchus; however, a sleeve operation was required because of air leakage from the bronchial stump. Lymph

Table 1 Summary of sleeve pneumonectomy cases

Patient	Indications	Side for surgery	Age/sex	Histopathology	Stage	Preoperative therapy	Reason for salvage surgery	Complications	Outcomes (months)
1	non-salvage	Right	60/M	LCNEC	IIB	-	-	-	Cancer death (3)
2	non-salvage	Left	69/M	Adenocarcinoma	IIIA	-	-	-	Cancer death (21)
3	salvage	Right	73/M	Squamous cell carcinoma	IIB	CRT	Hemoptysis	Af	Cancer death (4)
4	non-salvage	Right	66/M	Squamous cell carcinoma	IIIB	-	-	-	ADf (159)
5	non-salvage	Right	44/M	Adenocarcinoma	IIIB	-	-	Sinus tachycardia	Cancer death (3)
6	non-salvage	Right	43/F	Adenoid cystic carcinoma	IIIB	-	-	b.p fistula	Cancer death (11)
7	salvage	Right	58/M	Small cell carcinoma	IIB	CRT	Obstructive pneumonia	-	Cancer death (2)
8	salvage	Right	48/M	Metastatic colon carcinoma	-	chemotherapy	SVC syndrome	-	Cancer death (12)
9	non-salvage	Right	48/M	Squamous cell carcinoma	IIIB	-	-	-	ADf (136)
10	non-salvage	Right	67/M	Adenoid cystic carcinoma	IIIB	-	-	Af	Cancer death (7)
11	non-salvage	Right	66/M	Squamous cell carcinoma	IIIA	-	-	b.p fistula Empyema Pneumonia	exitus due to respiratory failure (2)
12	non-salvage	Left	78/F	Adenoid cystic carcinoma	IIIA	-	-	-	Cancer death (54)
13	non-salvage	Right	73/M	Pleomorphic carcinoma	IIIA	-	-	-	ADf (104)
14	salvage	Right	56/F	Metastatic leiomyosarcoma	-	-	Hemoptysis Obstructive pneumonia	Af	Cancer death (4)
15	salvage	Right	70/M	Adenocarcinoma	IIIB	-	SVC syndrome	Af	Cancer death (9)
16	non-salvage	Right	58/M	Squamous cell carcinoma	IIIA	-	-	b.p fistula Af	exitus due to pneumonia (42)
17	salvage	Right	66/M	Squamous cell carcinoma	IIB	CRT	Progressive disease	Af	Cancer death (12)
18	salvage	Right	47/M	Pleomorphic carcinoma	IIIB	-	t.e fistula	b.p fistula Empyema	Cancer death (6)
19	non-salvage	Right	57/M	Squamous cell carcinoma	IA	-	-	-	ADf (73)
20	non-salvage	Right	65/M	Squamous cell carcinoma	IIIA	-	-	Pneumonia	Cancer death (7)
21*	salvage	Right	65/M	Squamous cell carcinoma	IIIA	RT	stable disease	-	ADf (58)
22	salvage	Right	48/M	Squamous cell carcinoma	IIIA	CRT	t.e fistula post CRT	-	ADf (56)
23	salvage	Right	70/M	Squamous cell carcinoma	Rec.	CRT	Obstructive pneumonia	b.p fistula Af Empyema Anastomotic stenosis	exitus due to respiratory failure (43)
24	salvage	Right	45/M	P/D Carcinoma	-	CRT	t.e fistula post CRT	b.p fistula Empyema	exitus due to respiratory failure (1)
25	non-salvage	Right	77/M	Combined small cell carcinoma and squamous cell carcinoma	IIIB	-	-	b.p fistula	ADf (14)
26	salvage	Right	78/M	Squamous cell carcinoma	IIB	-	Obstructive pneumonia	-	Cancer death (6)
27	non-salvage	Right	56/M	Squamous cell carcinoma	IIIB	-	-	-	ADf (12)
28	salvage	Right	64/M	Pleomorphic carcinoma	IIIA	-	SVC syndrome	AE-IP	Cancer death (6)
29	salvage	Right	70/F	Adenocarcinoma	IVA	CRT	Radiation pneumonitis	b.p fistula AE-IP	exitus due to respiratory failure (1)
30	salvage	Right	72/M	Squamous cell carcinoma	IIA	CRT+ICI	ILD related ICI	AE-IP Anastomotic stenosis	exitus due to Anastomotic stenosis (6)
31	salvage	Right	67/M	Squamous cell carcinoma	Rec.	CRT+ICI	Local recurrence	-	ADf (8)
32	salvage	Right	62/F	Squamous cell carcinoma	IIIB	CRT+ICI	Progressive disease	-	ADf (5)
33	salvage	Right	67/M	Squamous cell carcinoma	Rec.	CRT+ICI	Local recurrence	-	ADf (1)
34	salvage	Right	43/M	Squamous cell carcinoma	Rec.	Lobectomy	Local recurrence	-	ADf (1)

*This patient underwent SP as salvage therapy.

LCNEC, large cell neuroendocrine carcinoma; Rec, recurrence; CRT, chemoradiotherapy; RT, radiotherapy; ICI, immune checkpoint inhibitor; SVC syndrome, Superior vena cava syndrome; t.e fistula, tracheoesophageal fistula; ILD, Interstitial lung disease; b.p fistula, bronchopleural fistula; AE-IP, acute exacerbation of interstitial pneumonia; Af, Atrial fibrillation; ADf, Alive and disease-free; P/D, poorly differentiated.

node #7 was swollen to 72 mm and macroscopically N2, but pathologically negative. In case 19, a lesion was present in the lumen of the right main bronchus from B6. It was 5 mm away from the carina. Although there was no invasion at the tracheal bifurcation, SP was required because there was insufficient distance to close the bronchial stump. We identified the tumor as T1 as described in the TNM classification of lung carcinomas, "The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall is classified as T1." Case 21 was judged inoperable by another hospital and was scheduled for chemotherapy after radiation therapy. However, before chemotherapy, the patient visited our hospital for a second opinion and underwent salvage surgery. Hilar lung cancer in case 24 was discovered due to dysphagia and coughing. The patient was diagnosed with Stage IIIB disease at the hospital of origin and received chemoradiotherapy followed by durvalumab. The patient was referred to our hospital with an esophageal–tracheal fistula. Right sleeve pneumonectomy with esophagectomy, cervical esophagostomy, and enterostomy was performed. Four days after the operation, a tracheobronchial anastomotic fistula developed, and reoperation was performed. We excised the old anastomotic site, anastomosed the trachea and bronchus at the new site, and covered it with the omentum. Although there was no problem with the anastomotic site, respiratory failure subsequently occurred, and the patient was lost on postoperative day (POD) 18 after the first operation. Postoperative pathology revealed no tumor cells after chemoradiotherapy. Patient 31 underwent sleeve right upper lobectomy by a previous doctor and was administered cisplatin and vinorelbine as adjuvant chemotherapy. Subsequently, local recurrence was diagnosed and chemoradiotherapy and then durvalumab were administered. Pembrolizumab was administered because it was diagnosed as recurrence by PET/CT. However, the tumor grew and the patient was referred to our hospital. Salvage SP was performed, and the patient was discharged without complications. Bronchoscopy revealed healing of the tracheobronchial anastomosis on POD 6 and 55 (Figure 1) without any problems, even after chemoradiotherapy.

Table 2 summarizes the comparison of the characteristics between salvage and non-salvage SP. In the non-salvage SP group, 13 (87%) of patients were men with an average age of 63.1 years and 13 (87%) underwent surgery on the right side. In the salvage surgery group, 16 (84%) patients were men with an average age of 61.5 years; all patients underwent surgery on the right side. Distant metastases were not observed in either group. The T-factors of salvage surgery were unreported in certain pathological reports because the salvage group included metastatic leiomyosarcoma, meta-

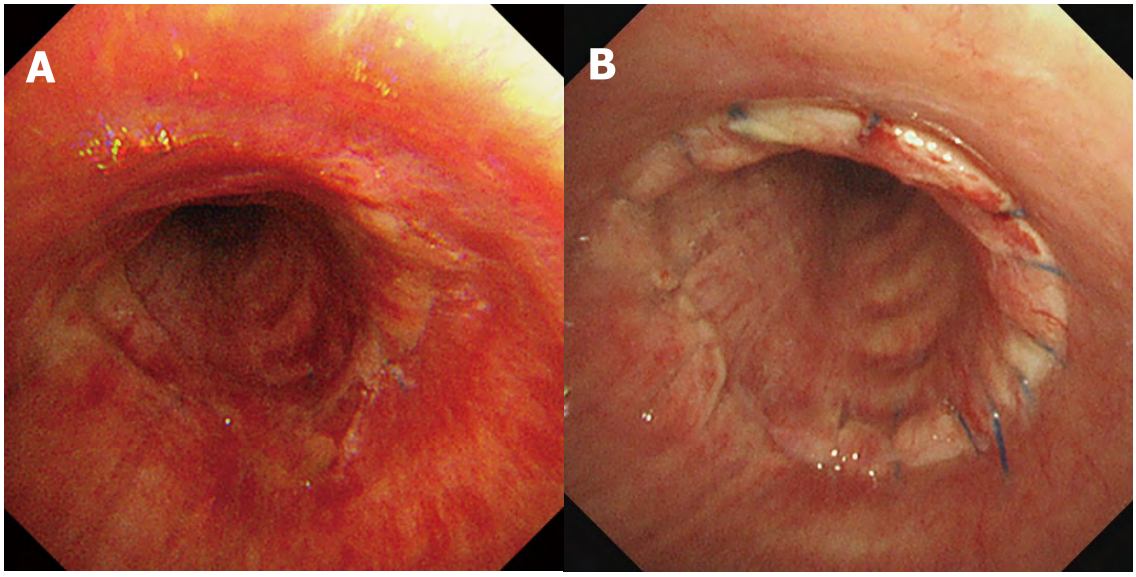

Figure 1 Case 31 underwent salvage sleeve pneumonectomy after chemoradiotherapy. Bronchoscopy showing healing of the tracheobronchial anastomosis on postoperative day 6 (A) and 55 (B).

Table 2 Characteristics of the patients

Characteristics	Non-salvage (N=15)	Salvage (N=19)
Age	43-78 (63.1)	43-78 (61.5)
Sex		
Female	2	3
Male	13	16
Side		
Left	2	-
Right	13	19
Comorbidities		
Diabetes	2	1
Hypertension	1	2
Cerebral infarction	2	-
Arrhythmia	1	-
Chronic kidney disease		1
Dyslipidemia	1	1
Post PCI		1
T status		
1	-	-*
2	1	1*
3	4	3*
4	10	6*
N status		
0	4	7*
1	2	5*
2	9	5*
M status		
0	15	19
1	-	-
Pathology		
Squamous cell carcinoma	7	11
Adenocarcinoma	2	2
Pleomorphic carcinoma	1	2
Adenoid cystic carcinoma	2	-
Other	3	4
Combined resection		
Superior vena cava	1	7
Left atrium	2	1
Esophagus	-	3
Left brachiocephalic vein	-	2
Azygos vein	-	1
Preoperative treatment		
Chemoradiotherapy	-	11
Radiotherapy	-	1
Chemotherapy	-	1
Morbidity	7 (47%)	10 (53%)
Mortality 30 day	-	2 (11%)
Mortality 90 day	3 (20%)	3 (16%)

PCI: percutaneous coronary intervention
* The T-factors and the N-factors of salvage surgery were not reported in some pathological reports because the salvage group included metastatic leiomyosarcoma, metastatic colon carcinoma, post-CRT cases, and recurrence cases.

static colon carcinoma, post-CRT cases, and recurrence cases. In cases of non-salvage SP, only the SVC and left atrium were resected. However, in the salvage surgery cases, there were additional cases of combined resection of the esophagus, left brachiocephalic vein, and azygos vein. No intraoperative mortality occurred. In the salvage group the 30-day mortality was 11% (2 of 19): respiratory failure after bronchopleural fistula, 1; respiratory failure after bronchopleural fistula and acute exacerbation of interstitial pneumonia, 1.

Table 3 summarizes the postoperative morbidity between the salvage and non-salvage SP groups. Complications occurred in 47% of the non-salvage SP and 53% of the salvage SP cases. Bronchopleural fistula occurred in 27% of the non-salvage SP and 21% of salvage SP cases. In contrast, anastomotic stenosis was only observed in the salvage group (11%; 2 of 19).

Discussion

Indications for sleeve SP are relatively uncommon and have been largely applied solely at specialized thoracic surgery centers. This lack of experience has led to unfamiliarity with the indications and results of tracheobronchial resection, frequently preventing it from consideration as a viable treatment option. Indeed, these tumors are often considered "unresectable" and treated with chemotherapy or chemoradiotherapy. Despite the complex technical challenges and risks associated with carinal resection, it offers patients a chance for long-term survival when the alternatives are simply palliative[5]. Furthermore, salvage surgery—that is, surgery for recurrence or tracheoesophageal fistula after definitive CRT—is technically demanding and can lead to serious anastomotic complications. However, preoperative thoracic radiation is no longer considered a contraindication to resection[6]. Our institute previously reported salvage surgery after definitive CRT in 27 patients with NSCLC. The median administered radiation dose was 60 Gy. Pneumonectomy was performed in nine patients, including two carinal resections, and lobectomy was performed in 18 patients, including five bronchoplasties. Although arrhythmia was observed more frequently in patients who underwent bronchoplasty, bronchopleural fistulas were found in only two patients who underwent pneumonectomy.

Table 3 Postoperative morbidity

Complications	Non-salvage (N=15)	Salvage (N=19)
Total	7 (47%)	10 (53%)
Arrhythmia	3 (20%)	5 (26%)
Bronchopleural fistula:	4 (27%)	4 (21%)
Empyema	1 (7%)	2 (11%)
Pneumonia	2 (13%)	-
Anastomotic stenosis	-	2 (11%)
Acute exacerbation of interstitial lung disease	-	2 (11%)
(Broncho-pleural fistula related)	-	1 (5%)

Salvage surgery after definitive CRT is acceptable for NSCLC. Bronchoplasty or pneumonectomy should be considered as options, even after the administration of high-dose CRT[7].

Case 22 was previously reported in detail as a case report. Tracheoesophageal fistulae are among the most serious complications that occur during curative chemoradiotherapy for advanced lung cancer. Generally, tracheoesophageal fistulas have extremely poor prognosis, and most treatments are palliative; however, the patient recovered without major postoperative complications[8].

The overall morbidity after carinal resection or sleeve pneumonectomy ranges from 11% to 50%[9]. Atrial fibrillation (AF) was seen in 17 cases and is a common complication after pneumonectomy that is relatively benign, easy to treat, and typically reversible. Mansour et al. reported no adverse effects from AF in patients with this complication. AF has not been found to result in prolonged postoperative hospitalization[10]. One of the most challenging complications is acute respiratory distress syndrome (ARDS), which occurs in up to 20% of patients and has an associated mortality of 50-100%. The incidence of bronchopleural fistula (BPF) in carinal sleeve resections is generally within the range of 3.8-21.6% in the literature. BPF is a serious complication and is among the most common causes of morbidity and mortality[11]. Post-pneumonectomy BPF is seen more often after right pneumonectomy and is clinically more severe than that observed after a lobectomy, with a mortality rate ranging from 25 to 71%[12, 13]. Typically used treatment methods include tube thoracostomy, open window thoracostomy, thoracomyoplasty, closure of the fistula with rethoracotomy and reinforcing the stump with live autologous flaps, and transpericardial closure of the fistula with sternotomy[11-14]. We encountered an anastomotic fistula in eight cases. One patient underwent chest drainage, but was subsequently lost due to acute exacerbation of interstitial pneumonia. Seven cases recovered with surgery: fenestration, or re-suturing and covering with an intercostal muscle flap or anterior mediastinal fat tissue. Some salvage cases had a poor prognosis; however, most of the deaths were due to cancer, and there were no problems with the indications for surgery. A notable feature of our study was the high frequency of salvage SP after recurrence, definitive CRT, and symptoms such as hemoptysis that must be treated. It has been reported that the mortality rate of pneumonectomy after CRT is 24% in North America and is considered almost contraindicated[15]. Case 31 was a salvage case for recurrence after postoperative CRT. As mentioned previously, no complications occurred at the anastomotic site. Therefore, post-CRT did not result in surgery not occurring. Non-salvage cases are treated to achieve a complete cure; however, salvage cases include progressive diseases after definitive CRT, hemoptysis, obstructive pneumonia, SVC syndrome, and tracheoesophageal fistulas post-CRT. As such, no other treatment options are currently available. Morbidity was relatively high (47%, non-salvage; 53%, salvage), but in our study the 30-day mortality was zero for non-salvage and 11% for salvage. We believe that it is an option for improving quality of life (QOL) through longer desease-free survival (DFS) and alleviation of symptoms rather than waiting for tumor growth progression and exacerbation of symptoms.

This study was limited by its single-center retrospective design. Additionally, only patients who

underwent surgical resection were enrolled. Almost all patients in our study were initially treated at different institutions and were selected for the evaluation of salvage surgery for different reasons, reflecting the heterogeneity of the population and treatment approaches. Nevertheless, this study provides new information regarding the surgical options for salvage sleeve pneumonectomy. Further studies with larger sample sizes are required.

Conclusions

Further research is necessary to determine appropriate indications for this challenging procedure; however, salvage sleeve pneumonectomy after chemoradiotherapy or in the presence of urgent symptoms is feasible with acceptable mortality and morbidity and promising long-term results.

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Author contributions

All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declares that there are no conflicts of interest.

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Case Reports

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Germ Cell Neoplasia in Situ Recognized Incidentally with Complaining of Discomfort in the Right Testis: A Case Report

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A 27-year-old man experienced discomfort in his right testis in early September, 2021, and visited the hospital five days later. Physical examination did not detect any abnormalities in the scrotum. However, an ultrasound revealed a tumor in the central part of the right testis, and a Magnetic Resonance Imaging (MRI) showed a tumor 2.7cm in diameter with clear boundaries and a marginally smooth surface.

The level of alpha-fetoprotein, human chorionic gonadotropin, human chorionic gonadotropin-β subunit, and lactate dehydrogenase were within normal limits. A Computed Tomography (CT) scan showed no abnormalities. We can't rule out the possibility of malignancy, right radical orchiectomy was performed with a diagnosis of right testicular tumor in mid-September 2021.

The macroscopic lesion was 1.5×1.3 cm in size, and no viable tumorous cells were found pathologically. Atypical cells were observed in the seminiferous tubules from the spermatic cord, which were positively stained with immune-histochemical staining CD117 (c-kit), D2-40, and MIB-1 but negatively with alpha-fetoprotein, human chorionic gonadotropin, and human chorionic gonadotropin-β subunit.

The pathological diagnosis was germ cell neoplasia in situ, and no continuity was observed between these cells and bleeding necrosis.

The patient has been followed up for 1 year and 4 months after surgery, with no recurrence or metastasis observed.

Key words: testicular cancer, germ cell neoplasia in situ, testis

Introduction

Recently, germ cell neoplasia in situ (GCNIS) has been well recognized as a precursor lesion to testicular germ cell tumor. Although GCNIS is frequently found in association with germ cell tumors such as seminoma, isolated reports of GCNIS are relatively rare in the literature. In this report, we present a case of GCNIS incidentally discovered in a patient who presented with discomfort in the right testis. We also provide a review of previously reported cases of GCNIS.

Case report

A 27-year-old man presented with discomfort in the right testis in early September, 2021 and visited our department shortly thereafter. No abnormalities were found on palpation of the scrotum. Ultra-

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sound revealed heterogeneous neoplastic lesion in the central part of the right testis (Figure 1). MRI revealed 2.7cm clear boundary and marginally smooth tumor in the center of the testis (Figure 2). Alpha-fetoprotein level was 1.38 ng/ml, human chorionic gonadotropin level was less than 1.0 mIU/l, human chorionic gonadotropin-β subunit level was less than 0.1ng/ml, and lactate dehydrogenase level was 178 U/l. CT revealed no abnormalities. We can't rule out the possibility of malignancy, right radical orchiectomy was performed with a diagnosis of right testicular tumor in mid-September 2021. The cut surface showed a solid mass 1.5cm in diameter in the right testis (Figure 3).

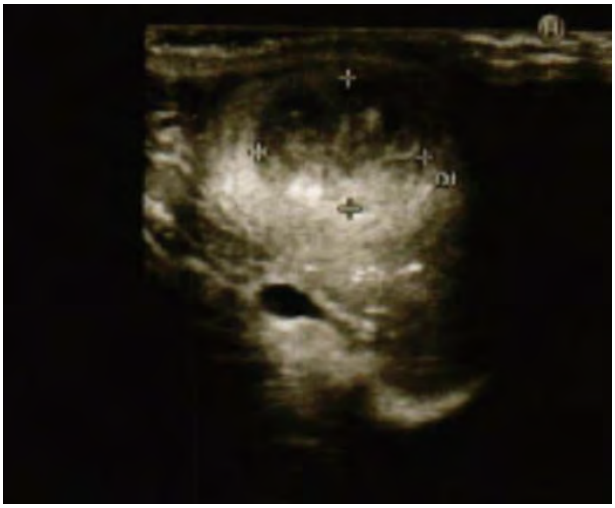

Figure 1 Ultrasound reveals heterogeneous neoplastic lesion in the right testis

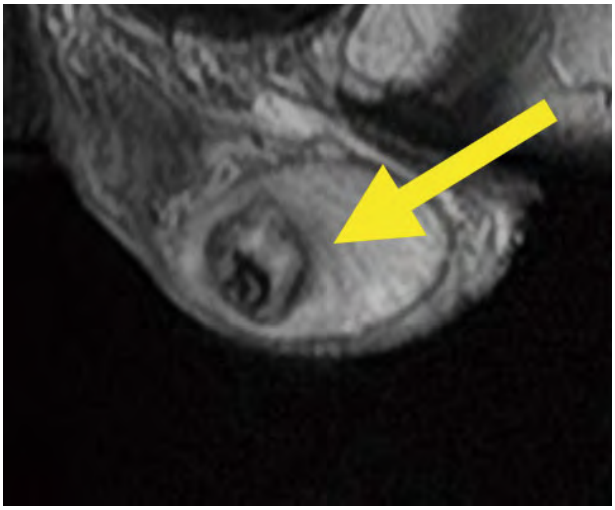

Figure 2 MRI reveals 2.7cm in diameter, clear boundary, and marginally smooth tumor in the right testis

Bleeding necrosis and granulation tissue were observed in the tumorous lesion, but no viable tumorous cell component was observed pathologically. The granulation tissue intervened on the boundary line between necrosis and existing testicular tissue, but no findings suggestive of a tumor were obtained (Figure 4). The lesion contained atypical cells that were observed in the seminiferous tubules from the spermatic cord. The atypical cells were like spermatogonia, large, and had clear reticulum. The nucleus had large irregularity and included a clear nucleolus. These cells were

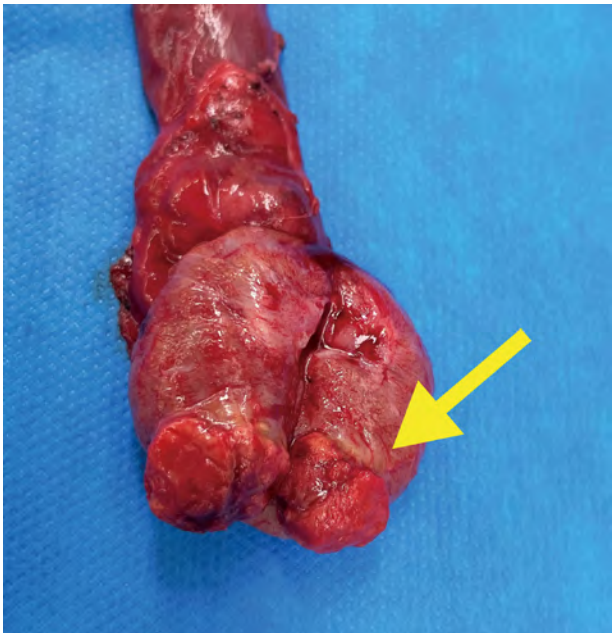

Figure 3 A solid mass 1.5cm in diameter in the right testis

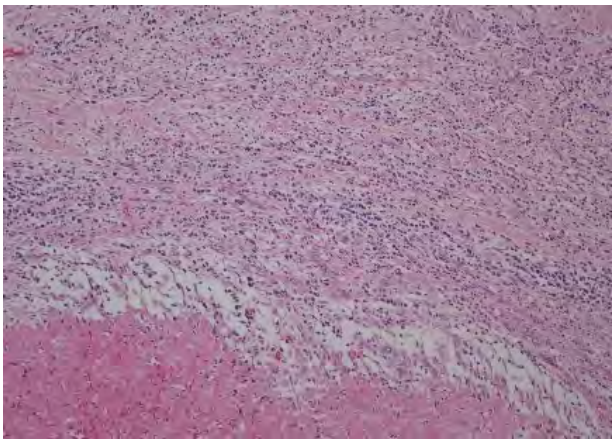

Figure 4 H&E staining × 100
Lower part is hemorrhagic necrosis area. No tumor was seen in the bordering granulation tissue.

arranged like lining the basement membrane. The collapse of the basement membrane or extravasation was not recognized. No extension to epididymis, vas deferens, and spermatic cord of atypical cells was seen (Figure 5). The surgical stump was negative for a tumor. The atypical cells were stained positively with immune-histochemical staining MIB-1 (Figure 6), CD117 (c-kit) (Figure 7) and D2-40 (Figure 8), but negatively with alpha-fetoprotein, human chorionic gonadotropin, and human chorionic gonadotropin-β subunit. No obvious continuity was observed between these cells and bleeding necrosis. From these results, the pathological diagnosis was germ cell neoplasia in situ (GCNIS). The patient's postoperative course was uneventful. After surgery, CT scans should be performed every 3 months according to the testicular tumor guidelines for the first year. Subsequently, CT scans should be conducted annually. He has no recurrence or metastasis 1 year and 4 months after surgery.

Discussion

World Health Organization (WHO) revised its classification regarding urinary tract and male genital tumors in 2016. One significant change was observed with testicular germ cell tumors. Until now, the histopathological classification of testicular germ cell tumors was based only on morphological similarities. In contrast, the new classifica-

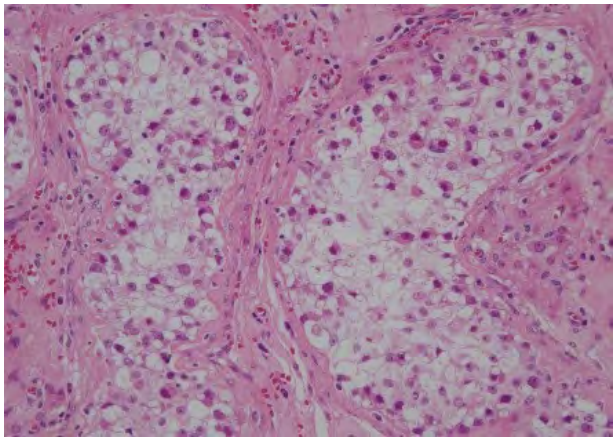

Figure 5 H&E staining × 200
Atypical cells do not extend beyond the basement membrane. Tumor cells are large, composed of a pale cytoplasm and large, irregular nuclei with well-defined nucleoli.

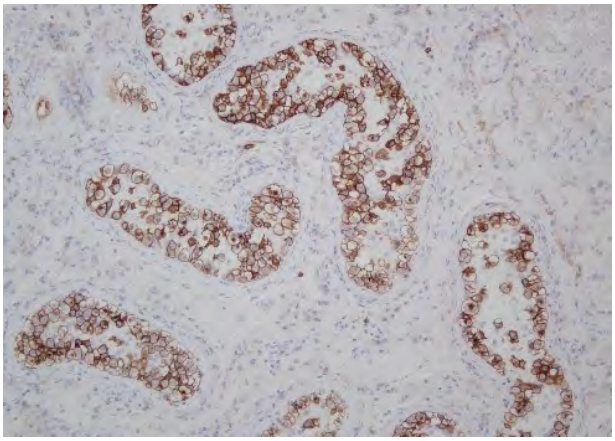

Figure 7 KIT (CD117) staining × 100
The tumor cell cytoplasm stains brown color. Consistent with GCNIS diagnosis.

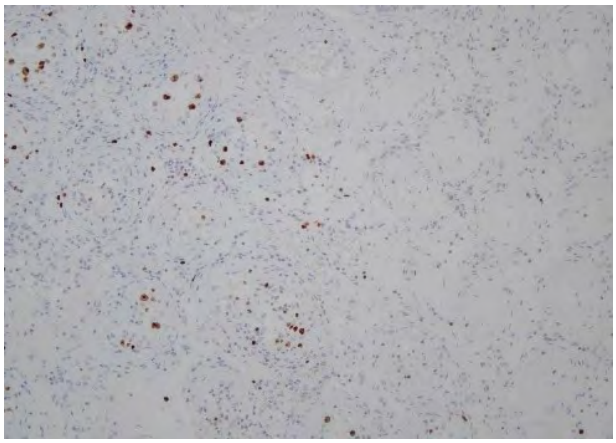

Figure 6 MIB-1 staining × 100
The tumor cell nuclei stain blackish brown color. 30-40% are positive, indicating cancer.

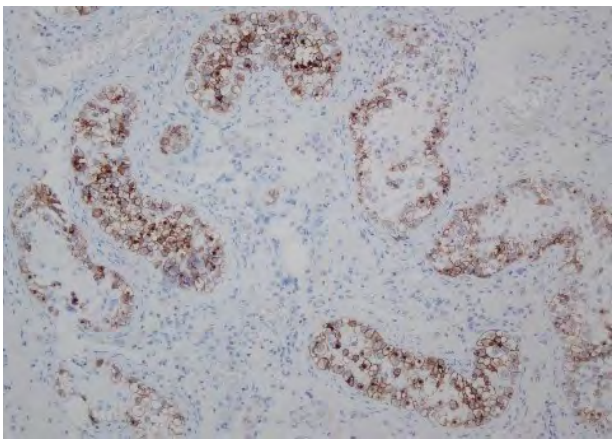

Figure 8 D2-40 (podoplanin) staining × 100
The tumor cell membrane stains brown color. Consistent with GCNIS diagnosis.

tion prioritizes similarities in histogenesis over morphological similarities. Germ cell neoplasia in situ (GCNIS), previously known as intratubular germ cell neoplasia of unclassified type, is now considered to be a precursor of most testicular germ cell tumors except for spermatocytic tumors, yolk sac tumors, and mature teratomas.

According to the general rule for clinical and pathological studies on testicular tumors, the 2018 4th edition, GCNIS is regarded as a large tumor cell similar to germ cells that appear sparsely or in a row on basement membrane. GCNIS cells stain positively with immune-histochemical staining such as Placental alkaline phosphatase (PLAP), CD117(c kit), OCT3/4, SALL4, and D2-40. In the current case, large tumor cells were recognized as standing in a row, and those cells stained positively with immune-histochemical staining MIB-1, CD117 and D2-40, but negatively with alpha-fetoprotein, human chorionic gonadotropin, and human chorionic gonadotropin-β subunit.

As far as searched in Japan, there were only three cases where testicular germ cell tumors were not recognized other than biopsy, and the tumor was GCNIS alone[1]. Testicular cancer occurs in 1% of men worldwide[2]. On the other hand, CNIS is a precursor lesion to testicular germ cell tumors, and there is a report that 50% of them in progress to testicular cancer in 5 years and 70% of them in 7 years[3]. There is a 1.9～5.2% chance that the testicular germ cell tumors occur contralaterally in heterochronous, and contralateral testicular biopsy during radical orchiectomy has been considered for the detection of GCNIS[4-6]. The frequency of identification in contralateral testicular biopsy has been reported to be 3～5%[7].

It has been pointed out that the risk of contralateral onset of GCNIS is high in cases with low semen concentration, small testis volume, irregular internal echo image of the testis, and young patients[8]. On the other hand, even if the result of contralateral testicular biopsy is negative, the development of tumors was about 1%, which can be considered a cause that the tumor was not detected due to low tumor burden[7, 9].

Two-part biopsy is considered to enhance the sensitivity of discovery. GCNIS was detected in 5.1% of prospective 2,318 case studies. The pathology of the biopsy specimens from the paired side was reported to be different in 31.1% of GCNIS-positive patients, and it was shown that the detection frequency increased with a two-part biopsy[10].

The complication rate of contralateral testicular biopsy includes hematoma and infection. The complication rate by two-part biopsy is reported to be less than 3%, and most complications resolved with conservative management, and the case requiring additional treatment was 0.6%[11]. The treatment of GCNIS is radiation therapy, which can result in a complete cure. However, due to differences in the radiosensitivity of testicular cells, only Sertoli cells remain in the seminiferous tubules, causing azoospermia. As Leydig cells have low radiosensitivity, hormone replacement therapy is often not needed[12]. It is reported that the an irradiation dose of 14 Gy causes 8% heterochronous incidence rate of germ cell tumor.

GCNIS will be 98% curable by irradiation dose of 18-20 Gy. But if the irradiation dose increases more than this, the possibility of hypogonadism will be increase.

Therefore, irradiation dose of 16-20 Gy is recommended for treatment[13]. Although contralateral testicular biopsy is not recommended in Japan, it may be considered in high-risk patients groups.

Because testicular cancer primarily affects young people, cryopreservation of sperm is an important consideration if radiation therapy is chosen. In such case, providing enough information to the patient and obtaining informed consent is necessary.

As this case involves a young patient and there is some possibility of contralateral onset, careful longer-term follow-up is required[14].

Conclusion

We described a case of GCNIS and reviewed the relevant literature. Since the patient is still young, longer-term follow-up is required.

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Author contributions

All authors read and approved the final manuscript.

Conflicts of interest statement

The Author declares that there are no conflicts of interest.

Informed consent

I obtained informed consent by providing an oral explanation of the study and receiving agreement from the participant.

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Perspectives

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Handgrip Strength and Healthspan: Impact of Sports During the Developmental Period on Handgrip Strength (Juntendo Fitness Plus Study)

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Handgrip strength as a biomarker is being studied as a factor in predicting disease onset. However, the effect of improving handgrip strength through physical exercises, such as sports during the developmental period, on disease prevention has yet to be fully elucidated. The Juntendo Fitness Plus (J-Fit Plus) Study is a unique database of anthropometric and physical fitness measurements with over 50 years of accumulated data. It has the potential to explore the effects of sports on the association between handgrip strength and morbidity/mortality. We first outline previous studies on the impact of physical exercise interventions on handgrip strength, separated into adulthood and developmental period. We then introduced a unique effort to investigate the effects of sports using the J-Fit Plus Study database and describe the challenges of finally elucidating the impact of exercise on the association between handgrip strength and health status.

Key words: grip strength, physical activity, kendo athletes, predicting future health

Introduction

Handgrip strength is a well-known biomarker of the aging process and health. Many studies have reported the health benefits of higher handgrip strength in middle-aged and older adults over the quarter of a century[1–4)]. For example, recent large-scale follow-up studies have repeatedly revealed the inverse association between handgrip strength and various diseases, such as heart diseases[1)], diabetes[2)], cancer[3)], and dementia[4)]. Although these analyses were adjusted for several covariates (age, education level, body mass index, alcohol, tobacco, medical history, etc.), the association still exists[1–4)]. In adolescents, low handgrip strength is also associated with poor cardiometabolic health outcomes[5)] and premature death[6)]. Therefore, achieving and maintaining a high level of handgrip strength may be useful[7, 8)]. However, low handgrip strength is observed across the lifespan[9)]. If improving handgrip strength through physical activity and sports is beneficial for future health, it may be helpful as a strategy for children and adults with low handgrip strength. Therefore, this perspective aims to discuss the following three points: 1) the impact of an exercise training intervention on handgrip strength in adults, 2) the impact of physical activity and sports on handgrip strength in children and adolescents, and 3) future research directions to elucidate the association between handgrip strength

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and health status.

Impact of exercise training intervention on handgrip strength in adults

Previous studies have examined the effects of nutrition alone, exercise alone, and combining the two on handgrip strength in middle-aged and older adults. For example, Bauer and colleagues[10] investigated the effect of dietary supplementation (i.e., vitamin D and leucine-enriched whey protein) on handgrip strength in 380 independent-living older adults. They reported that changes in handgrip strength did not differ from those in the control group after 13 weeks of the intervention. A meta-analysis has observed that nutrition alone has a small effect on handgrip strength (increased by 1.14 kg) compared to the control group[11].

On the other hand, Labott and colleagues[12] investigated the effects of exercise interventions on handgrip strength in healthy community-dwelling older adults of 60 years or older. They reported that the impact of exercise interventions, including aerobic and resistance training in different types or multi-dimensional training, was statistically significant, but the change in handgrip strength was small (standardized mean difference = 0.28). However, because this systematic review and meta-analysis include different modes of exercise training, it is necessary to consider the impact of resistance training alone, which might be particularly effective. Several systematic reviews and meta-analyses have recently reported the effects of resistance training on handgrip strength in older adults[13-15]. Surprisingly, the impact of resistance training on handgrip strength in older adults was small (the standardized mean difference was less than 0.3). These results suggest that handgrip strength is unlikely to improve with regular resistance training during late adulthood[16]. If this is true, it is thought that increasing handgrip strength as much as possible during the process of reaching young adulthood is effective in maintaining high handgrip strength during adulthood.

Incidentally, in the previous studies investigating the association between handgrip strength and morbidity, the morbidity was observed by dividing handgrip strength into three or four groups (e.g., low, mid, and high). In these studies, the differences in cutoff values or mean values between the low and high handgrip strength groups were approximately 10-15 kg[1, 3, 17, 18]. These values may help inform on what change might be required to see an improvement in handgrip strength (at least one that might be associated with health benefits). However, that is a value that needs to be updated through longitudinal studies. More importantly, it will be important to identify the minimum level of strength required for health (if any).

Impact of physical activity and sports on handgrip strength in children and adolescents

Resistance-type exercises for children and adolescents include lifting weights, bodyweight movements, and upper-body exercises performed during play from an early age. These physical activities are expected to contribute to developing upper-body and lower-body muscular strength, including handgrip strength for children and adolescents. A recent review[8] investigating the impact of physical activity and sports on handgrip strength in children and adolescents compared changes in handgrip strength in children engaged in extra physical activity and sports (i.e., intervention) to normal development (i.e., control). Types of interventions included family- and school-based physical activity and upper-body resistance training. The children and adolescents of the intervention groups increased the intensity and amount of physical activity at home or school, but no additional effects on handgrip strength were observed[8]. Similarly, boys and girls ages 7-12 who underwent eight weeks of upper and lower body resistance training had no additional improvement in handgrip strength[8]. This might suggest that using resistance training equipment for children is not enough of a stimulus for the agonist muscles of the finger flexors in the forearm and hand.

However, a recent study reported that handgrip strength might increase to a greater extent in those who participated in upper-body exercise (including gripping) during active play as children[19]. There are sports where players hold equipment in their hands and those in which they do not. Therefore, we were interested to know what types of sports are more effective for improvement in handgrip strength during the developmental period.

Fortunately, Juntendo University stores the results of handgrip strength measurements taken by students in school, and all first-year students undergo a handgrip strength test. This data only allows cross-sectional comparisons among sports events (i.e., an inability to know how much strength changed in response to the actual sport). However, first-year students usually have specialized in practicing one sport during their junior high and high school days.

Analysis using Juntendo Fitness Plus (J-Fit Plus) Study data

Faculty of Health and Sports Science, Juntendo University has conducted anthropometric, physical fitness, and motor ability measurements, including handgrip strength, as part of the university curriculum, and the test results have been available since 1973. We used the J-Fit Plus Study data from 1973 to 2018 to investigate the effects of the type of sports practiced on handgrip strength in first-year sport university students. The faculty of Health and Sports Science used to be exclusively male students until 1991, and the initial analysis used data only for males[20]. Privacy measures were maintained through Juntendo University, and all data were anonymized before analysis. We selected two types of sporting events with matching physiques (i.e., height and body mass), soccer (n=1127) targets the lower body, and kendo (n=297) and baseball (n=698) use the lower body simultaneously with upper body movement (including gripping). As a result, those in the lower body-only (soccer) sports had −3.78 (95% CI: −4.27, −3.29) kg lower handgrip strength than those in the lower + upper (kendo and baseball). Comparing each individual sport found that each sport was different from each other with kendo > baseball > soccer (between each sport, $p<0.001$)[20]. The difference in handgrip strength between kendo and soccer was about 5 kg in the overall sample, but the difference between the two groups has widened since the beginning of data collection.

Next, we tried a similar comparison using data from female athletes. The J-Fit Plus Study database from 1996 to 2018 includes 2301 first-year female students, and we selected two sporting events, i.e., soccer (n=161) and kendo (n=53). The mean and standard deviation of age, height, and body mass in the soccer and kendo groups was 18.3 (0.9) years old, 159.7 (5.5) cm and 54.8 (5.8) kg, and 18.1 (0.3) years old, 159.2 (5.2) cm and 58.0 (7.7) kg, respectively. The handgrip strength of female kendo athletes was 34.0 (4.3) kg, which was significantly higher than that of female soccer athletes [27.9 (4.4) kg; difference of 6 (95% CI: 4.7, 7.4) kg]. The results did not appreciably change after height and body mass adjustment. Although these findings are cross-sectional, our female and male results suggest that performing sports activities with upper-body gripping movements may be able to augment strength during the developmental years. It is noted that the sports we selected in this study are natural activities that do not directly train handgrip strength.

Future tasks

There are associations between handgrip strength and markers of health[1–6]. However, the overarching question is whether increasing handgrip strength would lead to an improvement in health. Unfortunately, there is not enough evidence at the moment.

In adults, gripping exercise may improve handgrip strength, but this might not influence an individual's health status[8]. At the same time, conventional (traditional) resistance exercise does not have a measurable influence[12–15]. Therefore, handgrip strength acquired in early adulthood is unlikely to change, except for the influence of aging and illness. In addition, it is reported that low to moderate intensity (30%–50% of maximal voluntary contraction) isometric grip exercise training is associated with decreased blood pressure in men and women[21]. However, this improvement in blood pressure is unlikely to be related to how strong (i.e., improving handgrip strength) someone can get. To the best of our knowledge, no studies have observed the impact of high-intensity grip training on risk factors for lifestyle-related diseases.

On the other hand, during the developmental period, sports such as kendo and baseball, which involve holding a tool with the hand, may positively affect the development of handgrip strength in children and adolescents[20]. However, one of the critical future issues is whether the improvement in

handgrip strength obtained by sports activity during the developmental period will change in later adulthood (especially the impact of stopping sports)[20]. In addition, the J-Fit Plus Study is cross-sectional data and does not compare the changes in handgrip strength in each sport during development, even though athletes have been engaged in a single sport. Thus, it is necessary to confirm whether participating in these sports is able to augment handgrip strength over that of normal development using a longitudinal design. Although our cross-sectional work suggests this, it is still possible that those with better handgrip strength self-select sports that require a gripping component (i.e., kendo). Finally, it is possible to observe the morbidity of various diseases and mortality using the difference in handgrip strength according to sports events recognized in the J-Fit Plus Study data. As these studies develop, it may be possible to clarify what utility handgrip strength has as a biomarker.

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Author contributions

TA, SM, JPL and HN have designed this study. YK, YS, KS, SM and HN have contributed to data collection. TA, YK and JPL have contributed to statistical analyses. TA wrote the first draft of the manuscript. All authors have contributed to the manuscript revision and read and approved the final version.

Conflicts of interest statement

There are no conflicts of interest to declare.

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Perspectives

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Understanding International Differences in Academic Author Order in General Medicine Publications

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Objectives: With increasing multinational research in general medicine, the lack of a standardized policy regarding the order of author bylines can create conflict and misunderstanding due to different practices worldwide.
Methods: We examined publicly available data from websites such as Journal Citation Reports and Web of Science, focusing on original articles published in the "Medicine, General, & Internal" category in 2020. Of 169 journals in the "Medicine, General, & Internal" category, we selected the ten countries with the highest number of publications and then examined the position of the corresponding author in the author byline as an indicator of the author in charge since corresponding authors are considered to have contributed the most.
Results: The top ten countries with the highest publications are the USA, China, Germany, England, Japan, France, Italy, Canada, India, and Australia. The results demonstrated that the percentage of the second author being the corresponding author was the highest in Japan compared to other countries. This percentage was 25 times higher in Japan than in the USA.
Conclusions: Understanding international differences regarding author order would facilitate smoother collaboration.
Key words: authorship, research, academia, publishing

Introduction

Recently, the importance of clinical research has been increasing. However, general practitioners or primary care physicians' contributions to clinical research have been somewhat limited compared to other specialists[1)], particularly in Japan[2)]. Historically, the role of primary care physicians has been defined by WHO as first-contact, accessible, continuous, comprehensive, and coordinated person-focused care, and is a key part of primary health care in achieving the goals stated in the "Health For All" in the Alma Ata Declaration[3)]. Owing to the establishment of general medicine as a medical board subspecialty in 2018[4)], the research contributions of primary care physicians are increasing, especially from younger primary care physicians.

Subsequently, it is imperative to promote high-quality and credible evidence-based research designs and international collaborations to conduct high-quality clinical research. Training and educating principal investigators play a major role in research institutions[5)], but the intricacy of unspoken rules regarding the author order (e.g.,

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first author, last author) are not covered in such training. In many countries, the order of authors in academic publications is as important as the impact factor of the journal in which they publish[6]. With increasing multinational research, the lack of a standardized policy regarding author order can create conflict and misunderstanding due to differing practices worldwide, hindering smooth collaboration[7]. Here, we studied author order in publications in different countries.

Methods

In this study, we used publicly available data from websites such as Journal Citation Reports and Web of Science, focusing on original articles published in 2020.

Discipline selection

Of the 178 fields registered in the Journal Citation Reports database, we selected "Medicine, General, & Internal" as our target discipline with 169 journals and examined the number of articles. We then selected the ten countries with the highest number of publications in the Web of Science: Science Citation Index Expanded database published from 2011 to 2020. We compared the number of publications in 2020 by country.

Order of author criteria

The corresponding authors are considered to have contributed the most since they are the primary correspondents with editorial offices and are responsible for decisions regarding manuscripts[8]. Therefore, we chose the corresponding author as an indicator of the author in charge. To determine the perceived credit of author order, we categorized the position in which corresponding authors are likely to be listed in articles such as 1) first author, 2) second author, 3) third author, 4) penultimate author, 5) last author, and 6) other position. We also set the following criteria: (1) to differentiate the first, second, penultimate, third, and last authors, we selected articles with more than five authors without group investigators; (2) we also selected articles with one corresponding author with one affiliated institution; and (3) we selected articles with the corresponding author affiliation and journal from the same country to evaluate the characteristics of countries with minimal influence from other countries. We then examined the position of the corresponding author in the author byline and compared countries.

Results

The top ten countries with the highest publications are the USA, China, Germany, England, Japan, France, Italy, Canada, India, and Australia (Table 1). Of the top ten countries, the USA, China, England, Japan, France, Italy, Canada, and India met the study's criteria. Seven journals were published in English, and three were published in the native language of the journal's country. The comparison of the corresponding author position by country is illustrated in Table 2. The percentage of second authors being corresponding authors by country was as follows: Canada = 1.8%, China = 3.8%, England

Table 1 Number of articles published in 2020

Country	Journal name	Articles published (2020)
Australia	International Journal of Medical Sciences	307
Canada	Canadian Medical Association Journal	86
China	Chinese Medical Journal	193
England	BMJ Open	2,678
France	Revue De Médecine Interne	60
Germany	European Journal of Clinical Investigation	168
India	Indian Journal of Medical Research	96
Italy	Acta Medica Mediterranea	590
Japan	Internal Medicine	454
USA	JAMA Network Open	1,026

Note. The right column shows the number of articles published by journals in the middle column in 2020.

Table 2 Summary of the corresponding author position by country

Country	Canada	China	England	France	India	Italy	Japan	USA
Author position	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
First	31 (56.4)	7 (4.5)	240 (70.6)	25 (56.8)	14 (23.7)	10 (30.3)	209 (51)	415 (71.4)
Second	1 (1.8)	6 (3.8)	15 (4.4)	3 (6.8)	11 (18.6)	6 (18.2)	124 (30.2)	7 (1.2)
Third	2 (3.6)	4 (2.5)	0 (0)	0 (0)	2 (3.4)	2 (6.1)	12 (2.9)	0 (0)
Penultimate	0 (0)	7 (4.5)	6 (1.8)	1 (2.3)	2 (3.4)	1 (3)	6 (1.5)	6 (1)
Last	21 (38.2)	129 (82.2)	76 (22.4)	15 (34.1)	27 (45.8)	11 (33.3)	56 (13.7)	152 (26.2)
Other	0 (0)	4 (2.5)	3 (0.9)	0 (0)	3 (5.1)	3 (9.1)	3 (0.7)	1 (0.2)
Total	55	157	340	44	59	33	410	581

Note. N represents the number of articles published by each journal in 2020, with articles that did not meet the selection criteria excluded.

= 4.4%, France = 6.8%, India = 18.6%, Italy = 18.2%, Japan = 30.2%, and the USA = 1.2% (Table 2).

Discussion

In this study of author order in general medicine journals, the results revealed different patterns of author order compared to Japan. The result demonstrated that the percentage of the second author being the corresponding author was the highest in Japan compared to other countries. This percentage was 25 times higher in Japan than in the USA. The second author holding the corresponding author position in Japan was greater than in other countries by the following factors: Canada = 16.6, China = 7.9, England = 6.9, France = 4.4, India = 1.6, Italy = 1.7, and the USA = 25.1. This finding aligns with the previous report that while the number of corresponding authors being first and last authors is higher in France, first and second authors being the corresponding authors is more common in Japan[9].

In Japan, laboratory chairpersons supervise Ph.D. students, but their priority is often securing research funds and laboratory management rather than guiding students in daily research. Instead, assistants or associate professors are likely to be the advisors for students. This suggests that the last author position may be reserved for chairpersons who provide research funds.

Although further research is needed, several possibilities can be speculated. First, the corresponding author in charge of directly guiding Ph.D. students' daily work is listed as the last author outside Japan. Second, as suggested above, supervising faculties take a second author position to give the chairperson the last author position. However, several publications as the corresponding author are essential for junior researchers' promotion opportunities, especially in becoming tenured professors in Japan. We speculate that chairpersons might designate junior researchers supervising Ph.D. students' daily research as the second author and corresponding authors for their future carrier path.

This study has several limitations. First, the data used for this study were from 2020, collected during the COVID-19 pandemic. Therefore, it might not be generalizable. Second, our study focused on general internal medicine journals, which may not be generalizable as it may not be a representative sample worldwide, including other clinical fields. Third, we did not differentiate between open-access journals and others, which could skew the results so that authors with funding were more likely to be listed as corresponding authors due to the Article Processing Charge.

In conclusion, academic author order in other disciplines and international journals should be examined further to clarify global norms and explore author order standards. In any case, multinational scientific collaborations are key to scientific breakthroughs and should be encouraged in any discipline or field, especially in medicine. Understanding international norms regarding the order of author bylines would facilitate smoother collaboration, especially in multinational research projects, and clarify the recognition of researchers' contributions.

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Author contributions

YN and SS conceived of the presented idea. YN developed the theory and YK and RU performed the computations. MS verified the analytical methods. MS, DA and YN analyzed and interpreted the data. MS, DA and YN were major contributor in writing the manuscript. YN and SS supervised. All authors discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Publication List

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〈Original Articles〉

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Psychiatry and Behavioral Science

〈Original Articles〉

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(Updated: October 19, 2023)

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Acknowledgments

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2) Matsumoto A, Arai Y: Hypothalamus. In: Matsumoto A, Ishii S, eds. Atlas of Endocrine Organs. Berlin: Springer-Verlag, 1992: 25-38.

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Summarize briefly the important points of the submitted work including a brief description of the study to be submitted, that it is an original study presenting novel work, that it has not been previously submitted to or accepted by any other journal, that is has been approved by all authors, and explain whether any author has a conflict of interest.

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編 集 後 記

今年は記録的な猛暑でしたが、ようやく過ごしやすくなり、論文を書いたり読んだりするのに最適の季節となってきました。最近の論文発表の状況は大きく変化し、いささかとまどいがあります。新規の科学雑誌が増加し、毎日何通も査読の依頼がありますが、見覚えのある雑誌はわずかです。馴染みの雑誌も、その評価が年々変化し、いわゆるインパクトファクター（IF）は、基礎系の雑誌はトップジャーナルを除くと大きく下落しています。一方、臨床系の雑誌の IF の上昇は驚くほどです。トップジャーナルに掲載される論文は、数十頁を超えるサプリメンタルデータが付属する分厚い論文が少なくなく、多くの著者、膨大な研究費と研究時間を要する研究が主体となり、研究の方法の変化も顕著です。しかし、これらの IF 超高得点雑誌に掲載された論文でも、再現性のない論文もあることはよく知られており、変化の激しい IF に右往左往させられる状況にはため息がでます。オープンジャーナル化は、便利性を高め、引用件数も増加させますが､論文掲載料の高さには閉口します。論文発表について色々考えさせられる中、講義資料をネット検索していたところ、J-stage で閲覧可能な「免疫学 100 年史」という川喜多愛郎先生の講演記事が検索トップに出てきました。川喜多先生は、伝染病を患って回復すると同じ病気にならないという法則 'non-rècidive' に「二度なし」という訳語を考案したことでも知られています。含蓄のある内容で、面白く読み進めていくと、なんと順天堂医学 28 巻 4 号（1982）に掲載された順天堂大学医史学開講 20 周年記念会特別講演の記事であることがわかりました。論文掲載について苦悩する中、順天堂医学（現在の順天堂醫事雑誌）が出版物として残していくことの重要性をあらためて思い出す機会をくれたことに、驚きと感動を覚えました。完全英文化された Juntendo Medical Journal は、このような機会を日本のみならず世界中に与えてくれることを期待しています。

三宅　幸子
医学部免疫学講座

イラスト作者より

もうすぐハロウィンなので、花屋の店先におもしろい柄や型のカボチャがたくさん並んでいました。全部本物だそうです。最近は、日本でも、このお祭りが定着したようですが、私もカボチャを描いてみたくなりました。（宮道明子）

順天堂醫事雑誌の記事については既に明治 8 年の創刊号から電子化されており，J-STAGE（科学技術情報発信・流通総合システム）の電子ジャーナル公開システムにおいて閲覧することができます．順天堂医学会のホームページからもご覧いただけますので，ご活用頂ければ幸いです（https://www.juntendo.ac.jp/journal/）．

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「順天堂醫事雑誌」では，医学界の最新知識を紹介するために，特集として総説を毎号に掲載しています．
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抄　録

順天堂醫事雑誌
2023. 69(5), 443

脳梗塞後軸索再生と機能回復の病態

上　野　祐　司[1, 2)]

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[2)]順天堂大学神経学講座

本邦における脳卒中の患者数は約 112 万人に達し，要介護となる原因疾患の第 2 位を占める．脳梗塞急性期では再灌流療法が普及したが，依然多くの患者が後遺症に苦慮しており，脳梗塞後の機能回復を目的とした治療法の確立は喫緊な課題といえる．脳梗塞後慢性期における軸索再生は，損傷後の組織再構築において重要な役割を担い，個体の機能回復とも関連する．筆者らは，ラット中大脳動脈閉塞モデルの peri-infarct area において，7 日後の急性期に脱落した軸索や樹状突起は 56 日後の慢性期では再生していることを確認した．In vitro では，虚血後軸索の再生には Phosphatase tensin homolog deleted on chromosome 10/Akt/Glycogen synthase kinase 3β シグナルが関わることを報告した．ラット慢性脳低灌流モデルでは，L-carnitine 経口投与により脳白質において軸索再生と oligodendrocyte の再生によるミエリンの肥厚が生じ，慢性脳虚血ラットの認知機能障害が改善した．近年，骨髄間葉系幹細胞由来のエクソソームによる脳梗塞後の組織再生効果が報告されている．脳梗塞後の軸索再生，機能回復のメカニズムは多岐にわたり，今後軸索再生を目的とした脳梗塞新規治療薬の開発，実用化が期待される．

キーワード： 脳梗塞，軸索再生，セマフォリン 3A，エクソソーム，機能回復

この抄録は，順天堂醫事雑誌 69 巻 5 号，p364-369，2023 掲載の『Mechanism of Post-stroke Axonal Outgrowth and Functional Recovery』の和文抄録です．

順天堂医学会 会員の皆様

順 天 堂 医 学 会
会長　服部　信孝

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

(1) 順天堂大学（大学院を含む）の学生で 1 か月以上 12 か月未満の海外留学をする者
(2) 留学先の研究機関または財団などからの援助がない者
(3) 医学会の正会員として 1 年以上の経歴を有し、医学会費を完納している者

2. 申請書類

(1) 順天堂医学会短期海外留学時助成金申込書
(2) 所属長の推薦書
(3) 申請者の主な研究テーマ・研究業績
(4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

留学期間	助成金額
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7 か月以上 12 か月未満	30 万円

4. 申請スケジュール（年 2 回）

申請期限	助成決定時期
6 月末	8 月
12 月末	2 月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

(1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。
(2) 帰国後は、順天堂大学またはその関連機関に原則として 3 年以上勤務する。

7. 本件の照会先

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