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順天堂醫事雜誌

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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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The Juntendo Medical Society

From the illustrator: Such a hot summer continues every day, which I might have experienced for the first time in my life. In order to make us feel even a little cooler, I drew a ceramic cat bathing its hind paws in a glass of water to cool off.

Perspectives

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A Personal Historical Perspective on Psychiatry in Japan During the Last 4 Decades

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After graduating from University of Tsukuba in 1982, I joined the Department of Psychiatry at the same university. Due to the anti-psychiatry social movement and reports of incidents involving violence against in-hospital patients at psychiatric hospitals, psychiatric associations in Japan faced questions related to ethical awareness, making it a challenging environment for conducting clinical research. For this reason, the first half of my journey—my 20 years at the University of Tsukuba—was spent conducting basic research on animal models of schizophrenia. With respect to the onset of schizophrenia, I studied dopamine and related neuropeptides in the brain, as well as abnormalities in neurotransmission in the excitatory and inhibitory amino acid neurotransmission systems.

In April 2002, I was appointed as a Department Chair at Juntendo University Koshigaya Hospital. I was responsible for overseeing many medical staff, including the clinical education of practicum students and resident physicians, as well as the training of psychiatric specialists. I was also involved in the management and operation of medical services provided at the mental health clinic that had 350 outpatients per day and saw the admission and discharge of 500 patients annually. Meanwhile, I became actively involved in activities related to perinatal mental health. In 2018, I was appointed as the Director of the Japanese Society of Perinatal Mental Health and worked diligently to improve medical care related to perinatal mental health in Japan through the development of perinatal mental health guidelines.

Key words: animal models of schizophrenia, Juntendo University Koshigaya Hospital, perinatal mental health, development of guidelines

Introduction

On the occasion of my retirement, I would like to impart some insights on my 40-year journey thus far and provide an overview of the transition that took place in the field of psychiatry in Japan during this period. After graduating from the School of Medicine, University of Tsukuba in 1982, I joined the Department of Psychiatry (chaired by Professor Junzo Koizumi) at the same university. Upon returning from studying abroad at the Department of Pharmacology and Toxicology at the University of Mississippi Medical Center (chaired by Professor Ing Kang Ho), I became an Associate Professor at the Department of Psychiatry, University of Tsukuba. In April 2002, under the Chief Professor, Dr. Heii Arai, I was appointed as a Department Chair at Juntendo University Koshigaya Hospital. In 2008, I became a professor (intradepartmental) at the Department of Psychiatry of Juntendo University Koshigaya Hospital which then led to my appointment as the Hospital Director at this hospital in April 2021, a position I still hold today.

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Basic research and clinical activities during my years at the University of Tsukuba

In the early 1980s, when I first started at the Department of Psychiatry, University of Tsukuba, Japan's psychiatric associations were experiencing the rippling effects of the anti-psychiatry social movement. The Japanese Society of Psychiatry and Neurology suspected several domestic clinical studies of ethical violations. Furthermore, even in the field of psychiatric care, reports of violent incidents perpetrated by mental health providers against in-hospital patients were surfacing. It was a time when these incidents concerning human rights issues involving psychiatric patients were being condemned. Associations in biological psychiatry, which developed into Japanese Society of Biological Psychiatry later, were forced to cancel their academic conferences in some years. This is why the Japanese Society of Psychiatry and Neurology established the "Committee on Research and Human Rights" in 1984 to monitor clinical research ethics. However, these were days during which the understanding with regard to research ethics in psychiatry was still undeveloped, and it was a challenging environment for conducting psychiatric clinical research. This historical backdrop significantly impacted the direction of my subsequent research life.

Research of abnormal neurotransmission systems in the brain in animal models of schizophrenia

After joining the department, I devoted myself to basic research, conducting animal experiments on schizophrenia models. Through repeated administrations of psychostimulants such as methamphetamine (MAP) to rats, we created rats that exhibited reverse tolerance or behavioral sensitization—the animal model of schizophrenia. My doctoral thesis focused on the cholecystokinin (CCK) system—a neuropeptide system that regulates dopaminergic neuronal systems—and I reported about the receptor abnormalities in the frontal cortex of the same nervous system.

In 1989, using the in vitro quantitative receptor autoradiographical technique, changes in the binding parameters of [propionyl-^{3}H] propionylated CCK-8 ([^{3}H]pCCK-8) binding sites in the rat forebrain were investigated following acute and chronic administration (14 days) of MAP (4mg/kg/day)[1]. The (Kd)app values of [^{3}H]pCCK-8 binding sites in the frontal medial cortex and anterior cingulate cortex were significantly reduced after a single injection of 4 mg/kg MAP. On the other hand, chronic treatment with MAP at this dose significantly decreased the B_{max} value of [^{3}H]pCCK-8 binding sites in the anterior cingulate cortex accompanied by supersensitivity of locomotor effects to MAP (Figure 1(A), (B)). These findings suggest that dopamine neurons in these two regions are functionally related to intrinsic CCK-containing cortical neurons, and that CCK subsensitivity, perhaps due to an alteration in DA transmission, is involved in MAP sensitization. These findings may be relevant to the DA hypothesis of schizophrenia.

While studying abroad in the United States (1995 to 1996) at the Department of Pharmacology and Toxicology, the University of Mississippi Medical Center, I researched the changes in gamma-aminobutyric acid (GABA)-benzodiazepine receptors in barbiturate dependence. During this process, I mastered the in-situ hybridization method, which led to my subsequent research on the role of receptor mRNA subunits.

In 1995, changes in benzodiazepine binding sites labeled by [^{3}H]flunitrazepam (FNZ) in twenty discrete brain regions of rats made tolerant to and dependent upon pentobarbital were examined[2]. Animals were rendered tolerant by intracerebroventricular infusion with pentobarbital (300 micrograms/ 10 microliters/hr for six days) through pre-implanted cannulae connected to osmotic mini-pumps. The pentobarbital dependence was assessed 24 hr after abrupt withdrawal from pentobarbital. In the tolerant rats, a significant increase in [^{3}H]FNZ binding sites was found in the frontal cortex and the molecular layer of olfactory bulb. [^{3}H]FNZ binding sites in the pentobarbital dependent rats were significantly increased in the frontal cortex, caudate-putamen, olfactory tubercle, globus pallidus and ventral pallidum, in addition to those observed in the tolerant group. Taken together with characteristics of subtypes of benzodiazepine receptors and changes in GABA-benzodiazepine receptor complexes elucidated in previous studies, these findings suggest that both types of benzodiazepine receptors are involved in the development

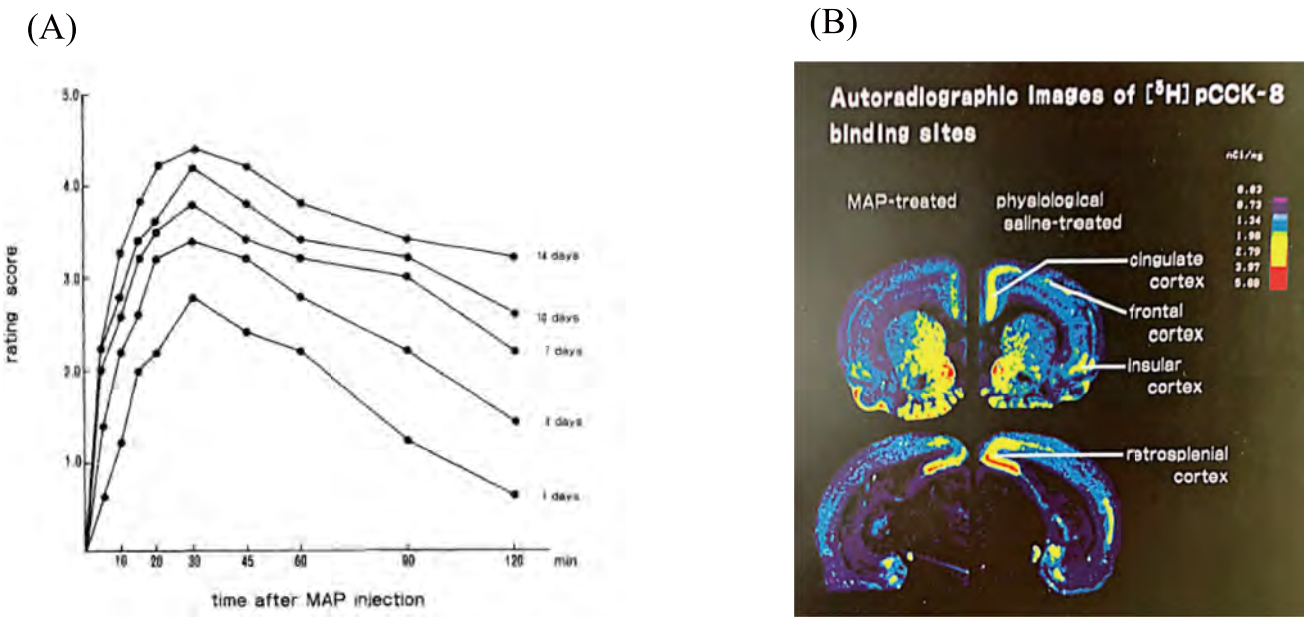

Figure 1 (A) The rating score after methamphetamine injection at every test session. The behavioral changes were manifested much more rapidly and the mean peak values were increased with the number of injections. It means behavioral sensitization or reverse tolerance (cited from ref. 1).
(B) Autoradiographic images of [^{3}H]pCCK-8 binding sites in the rat brain. Brain section images of physiologic saline-treated rats (on the right side) and those of methamphetamine-treated rats (on the left side) are shown (cited from ref. 1).

of pentobarbital intoxication mediated by $GABA_A$ receptors.

Upon returning to Japan, I conducted research related to receptor mRNA subunits of excitatory (glutamatergic) and inhibitory (GABAergic) amino acid neurotransmission systems in the brain of animal models of schizophrenia. At the time, the amino acid neural transmission was a research area of increased focus since antipsychotics, which are dopamine receptor blockers in drug therapy for schizophrenia, were not effective among some patients with positive symptoms and also lacked effectiveness against negative symptoms themselves.

In 2000, the effects of intermittent intraperitoneal (i.p.) administration of cocaine (20 mg/kg/day) on $GABA_A$-benzodiazepine (BZD) receptors labeled by t-[^{35}S]butylbicyclophosphorothionate (TBPS), and on several types of mRNA subunits were investigated in rat brain by in vitro quantitative receptor autoradiography (Figure 2(A)) and in situ hybridization (Figure 2(B))[3]. There was a significant decrease in the level of α1, α6, β2, β3, and γ2 subunits mRNA, with no alteration of [^{35}S] TBPS binding in any regions in the brain of rats at 1 h following a single injection of cocaine. In chronically treated animals, the mean scores of stereotyped behavior were increased with the number of injections. The level of β3 subunit mRNA was decreased in the cortices and caudate putamen, at 24 h after a final injection of chronic administrations for 14 days. These findings suggest that the disruption of $GABA_A$-BZD receptor formation is closely involved in the development of cocaine-related behavioral disturbances. Further studies on the physiological functions on $GABA_A$-BZD receptor complex will be necessary for an explanation of the precise mechanisms underlying the development of hypersensitization of cocaine.

In 2001, the following animal studies regarding phencyclidine (PCP), which induces psychotic symptoms in humans, have suggested that metabotropic glutamate receptors (mGluRs) represent a novel target for the treatment of PCP psychosis. We used in situ hybridization to investigate the gene expressions of the mGluR 1-5 subtypes following repeated administration of PCP in rats[4]. After repeated PCP administration for 14 days, the mGluR2 mRNA expression of group II mGluR in the anterior cingulate cortex and the mGluR4 mRNA expression of group III mGluR in the cortical regions, the caudate putamen, thalamus, and subiculum were significantly decreased (Figure 3).

(A)

(B)

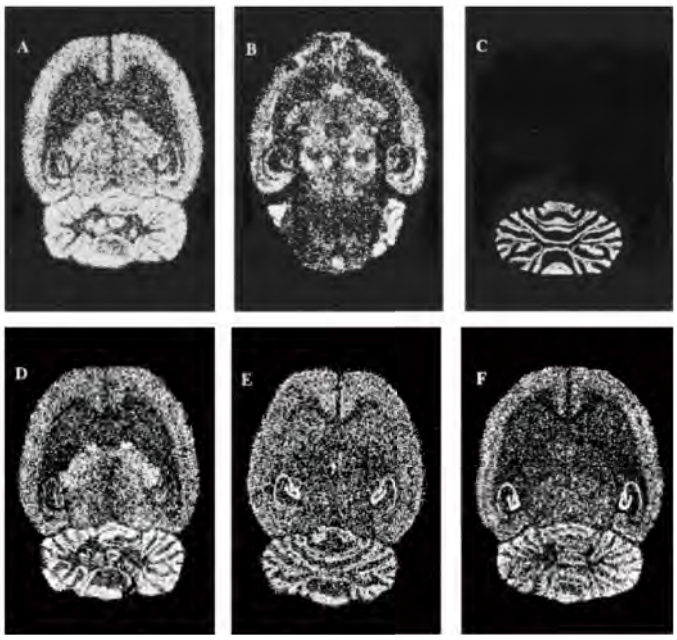

Figure 2 (A) Autoradiographic images labeled by [^{35}S]TBPS in rat brain published on the cover of the journal "Molecular Brain Research" (cited from ref. 3).
(B) The distributions of mRNAs of each of α1 (upper portion) (A), α2 (lower portion) (B), α6 (C), β2 (D), β3 (E), and γ2 (F) subunits. Each mRNA subunit shows a differential distribution (cited from ref. 3).

These results indicate that it is of particular interest that mGluR2 and mGluR4subtype is involved in a development of behavioral abnormality following repeated PCP administration.

In 2002, we subsequently investigated the effects of i.p. injections of cocaine (20 mg/kg/day) on subunit mRNAs of *N*-methyl-D-aspartate (NMDA) receptors (NR1/NR2A-2C) in the rat brain by in situ hybridization using phosphor screen analysis[5]. The level of NR1 subunit mRNA significantly increased in hippocampal complexes 1 h after a single i.p. injection of cocaine. After repeated cocaine injection, the mean scores of stereotyped behaviour were increased with the number of injections. The level of NR1 subunit mRNA was obviously decreased in the striatum and cortices 24 h after a final injection following 14 days of subchronic administration. Levels of NR2B subunit mRNA were reduced in the cortices and striatum. These findings suggest that the disruption of NR1 and NR2B subunits in the discrete brain regions occurs under the cocaine-related behavioral abnormalities and would be closely implicated in the initiation and expression of behavioral sensitization induced by repeated cocaine administration.

A memorable clinical report

In the 1980s in Japan, case reports were more actively reported than large-scale clinical studies, and borderline personality disorder and eating disorders were attracting much attention. A personally memorable case for me was a patient who had long been diagnosed with schizophrenia. The results of a detailed examination revealed that this patient had mitochondrial encephalomyopathy, and this case appeared as a case report in an international journal below.

In 1989, the author reported a case of a 37-year-old man with mitochondrial encephalomyopathy[6]. The recurrent mental disorder with auditory hallucination, delusion of reference was the main remarkable symptom during the earlier stage of illness. These symptoms were regarded as a schizophrenia-like symptoms. The present case was finally diagnosed as mitochondrial encephalomyopathy with schizophrenia-like symptoms. Ragged-red fibers and crystalline inclusions in mitochondria were revealed by biopsy of the striated muscle of the patient (Figure 4 (A), (B)). Mitochondrial myopathy, encephalopathy, lactic

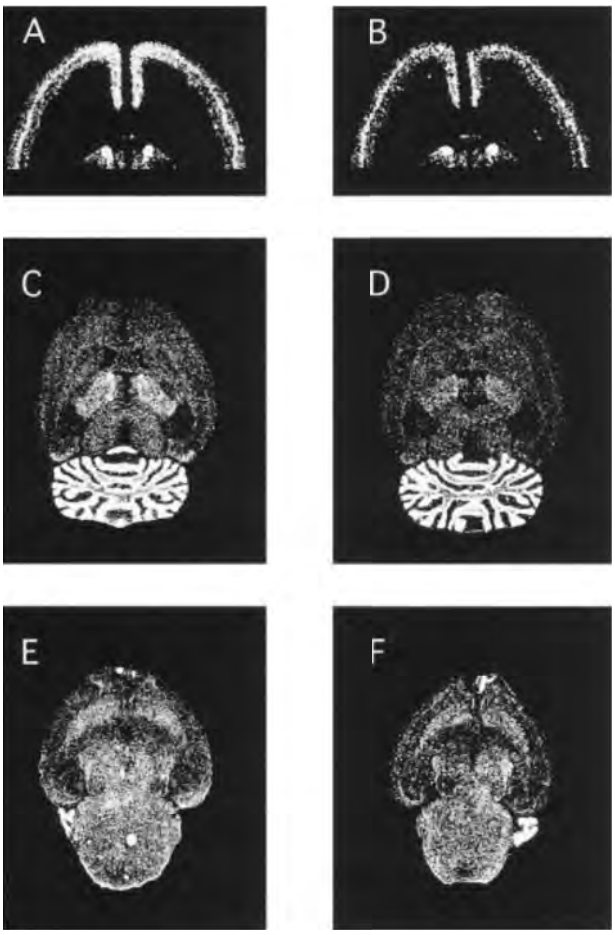

Figure 3 The autoradiograms of mGluR mRNA in horizontal upper and lower sections in rat brain after repeated administration. The left side (A, C, E) is treated with saline and the right side (B, D, F) is treated with phencyclidine (cited from ref. 4).

acidosis and stroke-like episodes (MELAS) was diagnosed clinically. In addition to severe atrophy and degeneration of the generalized striated muscles, many foci of laminar necrosis of the cerebral cortex and the abnormalities of general organs were observed. We suggested that mitochondrial encephalomyopathy can cause the organic brain syndromes showing schizophrenia-like mental symptoms.

Clinical activities and education at the Juntendo University Koshigaya Hospital and transitions in psychiatry

I joined the Juntendo University Koshigaya Hospital in April 2002, and for 21 years until my retirement, I served as a Department Chair and endeavored to enhance clinical activities and ensure medical safety at our hospital's mental clinic. Being a 226-inpatient-bed psychiatric hospital, we were committed to offering clinical education for the 5th grade medical students under the on site training and resident physicians and assisting young physicians aspiring to become psychiatrists in obtaining their qualifications as specialists and designated physicians (Figure 5). In the 2000s, a new trend swept across the field of psychiatry. In the field of psychiatric care, the concept of dementia started to gain attention. The Japanese name of the illness changed from "chihosho", which is a pejorative word for dementia, to "ninchisho", which is a descriptive

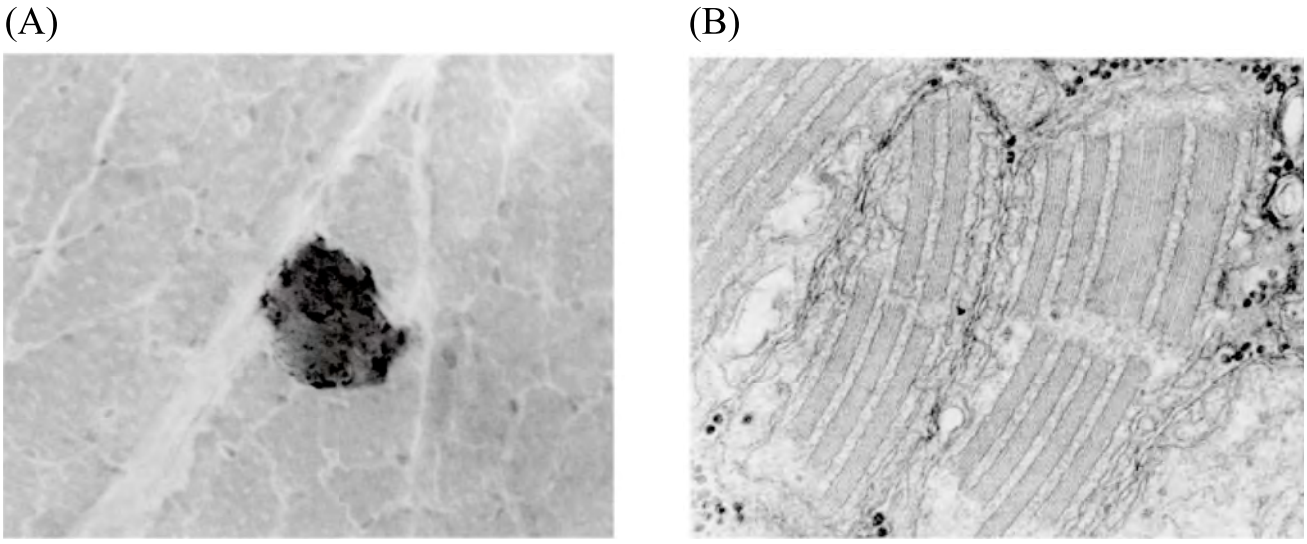

Figure 4 (A) Ragged red fibers with red granular material in the subsarcolemmal region from biopsied muscle tissue of the quadriceps. Modified Gomori-trichrome stain (cited from ref. 6).
(B) Electron microscopic examination revealed enlargement of mitochondria and aggregation of abnormal mitochondria with paracrystalline formation (x63000) (cited from ref. 6).

Figure 5 Medical staff in the Department of Psychiatry, Juntendo Koshigaya Hospital

word for neurocognitive disorder, and the therapeutic drugs for schizophrenia and depression transitioned from first-generation to second-generation therapeutic drugs. Further, in daily clinical practice, a decline in adverse events related to antipsychotics and antidepressants dramatically improved medication adherence, leading to more proactively conducting clinical studies on schizophrenia and depression than before. Our hospital also reported the results of a clinical study on depression. Less attention has been given to sex differences in the underlying biological mechanisms of depression. The adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S), play a critical role in controlling affect, mood, and anxiety.

In 2013, a clinical study examining the role of male sex hormones in depression is presented. The objective of the present study was to investigate differences in serum levels of adrenal androgens in male and female patients with major depressive disorder (MDD)[7]. Participants included 90 inpatients with MDD at the psychiatric ward of Juntendo University Koshigaya Hospital who were receiving antidepressants. Matched controls included 128 healthy individuals. Serum DHEA levels were significantly increased in both male and female MDD patients compared with controls. Serum levels of DHEA-S in male patients were significantly decreased compared with male controls. No significant correlations were seen between adrenal androgens and HAM-D scores in male or female patients. Multiple regression analysis showed that both hormones were affected by the age at onset of depression. Elevated levels of serum DHEA may be associated with the biological pathophysiology of depression, as DHEA administration has been found to be effective for the treatment of depression.

Contribution to perinatal mental health in Japan

In the field of psychiatry, and among the various areas therein, after 2010, a concept referred to as "unmet needs" began to draw attention. One of these areas was perinatal mental health in the psychiatry. In 2014, Juntendo University Hospital established an outpatient clinic specializing in perinatal mental health. At the time, this drew attention and was featured in the mass media (Figure 6). I was appointed as the Director of the Japanese Society of Perinatal Mental Health in 2018, and I have contributed many reviews in domestic journals about the challenges to and prospects for improving perinatal mental health in Japan. In

Figure 6 An outpatient clinic specializing in perinatal mental health was featured in the mass media. The photo (Oct. 27, 2014) is reprinted by courtesy of THE YOMIURI SHIMBUN.

2017, as the Deputy Chairperson, I was involved in creating the Consensus Guidelines on Perinatal Mental Health 2017 (Figure 7(A)). Through a joint collaboration between the Japanese Society of Psychiatry and Neurology and the Japan Society of Obstetrics and Gynecology, a committee was then formed to develop perinatal mental health guidelines. I served as the Chairperson of the Guidelines Preparation Committee, and the committee developed the overview in 2020[8] and subsequently the detailed contents in 2021[9] (Figure 7(B)). Recently, Guideline for pharmacological therapy of schizophrenia 2022 was created by the Japanese Society of Neuropsychopharmacology and the Japanese Society of Clinical Neuropsychopharmacology. (Figure 7(C)). I acted as an adviser in the field of perinatal mental health of schizophrenia.

Keeping in mind the limitations of animal disease models in the field of perinatal mental health, basic research was conducted with a focus on clinical conditions of perinatal mental health. In pregnant women with epilepsy, it is imperative to balance the safety of the mother and the potential teratogenicity of anticonvulsants, which could cause impairments such as intellectual disability and cleft lip.

In 2019, we examined behavioral and hippocampal neurogenesis alterations in male offspring of rats exposed to valproic acid (VPA) during pregnancy[10]. Pregnant Wistar rats received daily intraperitoneal injections of VPA (100 mg/kg/day or 200 mg/kg/day) from embryonic day 12.5 until birth. At postnatal day 29, animals received an injection of bromodeoxyuridine (BrdU). At postnatal day 30, animals underwent the open field (OF), elevated plus-maze, and Y-maze tests. Of the offspring of the VPA200 mothers, 66.6% showed a malformation. In the OF test, these animals showed locomotor hyperactivity. In the elevated plus-maze, offspring of VPA-treated mothers spent significantly more time in the open arms. The number of BrdU-positive cells in the dentate gyrus of the

(A) Perinatal mental health consensus guide 2017

(B) Clinical guide for women with mental health problems during the perinatal period

(C) Guideline for pharmacological therapy of schizophrenia 2022

Figure 7 (A) Perinatal mental health consensus guide 2017. The Japanese Society of Perinatal Mental Health, the Japan Association of Obstetricians and Gynecologists and the Japan Society of Obstetrics and Gynecology collaborated on this project.
(B) Clinical guide for women with mental health problems during the perinatal period. The guideline was created by cooperation of the following two fields, the Japanese Society of Psychiatry and Neurology and the Japan Society of Obstetrics and Gynecology. Overview in May 2020, and its Detailed Contexts in April 2021 have been reported, respectively.
(C) Guideline for pharmacological therapy of schizophrenia 2022. The guideline was created by the Japanese Society of Neuropsychopharmacology and the Japanese Society of Clinical Neuropsychopharmacology.

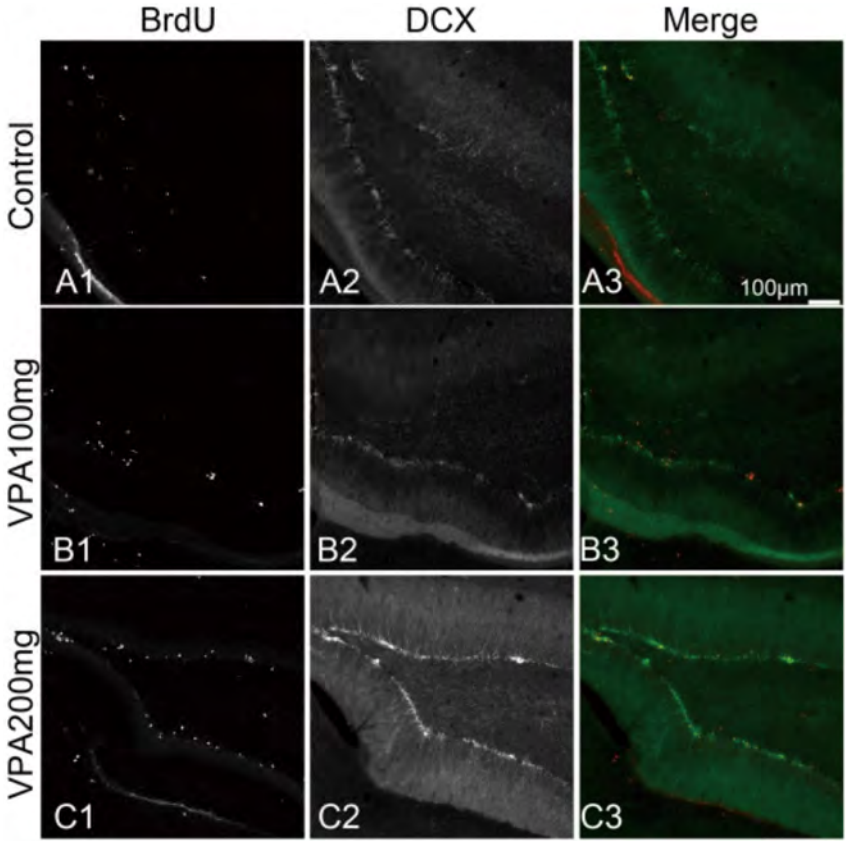

Figure 8 Hippocampal cell differentiation with BrdU and doublecortin(DCX) hippocampal dentate gyrus sections double immunostained for BrdU and DCX was shown (cited from ref. 10).

offspring of VPA-treated mothers increased significantly in a dose-dependent manner compared with the control (Figure 8). In conclusion, VPA administration during pregnancy results in malformations and attention-deficit/hyperactivity disorder-like behavioral abnormalities in the offspring. Repeated use of high doses of VPA during pregnancy may increase the risk of neurodevelopmental abnormalities dose dependently and should be carefully considered.

Conclusion

My 40 years as a psychiatrist were split into two phases: the first 20 years at the University of Tsukuba and the second 20 years at Juntendo University. Basic research was the focus during my days at the University of Tsukuba, while my activities at Juntendo University were concentrated on clinical research, education, and medical practice. I believe that the transition that I experienced as a psychiatrist reflects the changes of a psychiatrist who aspired to work in the field of biological psychiatry.

In April 2021, I was appointed as the Hospital Director at Juntendo University Koshigaya Hospital, where I have since been engaged in realizing a restructuring project. I plan to restructure the Juntendo University Koshigaya Hospital, a psychiatric hospital, into a general internal medicine hospital. From now on, I intend to focus my time on restructuring the Juntendo University Koshigaya Hospital from a psychiatric hospital into a new semi-general internal medicine hospital. I am committed to continue contributing to this development to the best of my capacity and aim to create a branding that sets us apart from other affiliated hospitals.

Acknowledgments

I would like to extend my deepest appreciation to all my mentors, peers, and senior and junior colleagues during my years at the University of Tsukuba and the Juntendo University and to all the staff at the Juntendo University Koshigaya

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Author contributions

TS contributed to the conception, drafting the manuscript, and preparation of figures.

Conflicts of interest statement

The author has no conflict of interest to disclose.

References

1) Suzuki T, Moroji T: Cholecystokinin binding sites in the rat forebrain: effects of acute and chronic methamphetamine administration. J Neural Transm, 1989; 77: 181–195.
2) Suzuki T, Ito T, Wellman SE, Ho IK: Change in [^{3}H] flunitrazepam binding in the rats made tolerant to and dependent upon pentobarbital. Life Sci, 1995; 57: PL63–69.
3) Suzuki T, Abe S, Yamaguchi M, *et al*: Effects of cocaine administration on receptor binding and subunits mRNA of $GABA_A$–Benzodiazepine receptor complexes. Synapse, 2000; 38: 198–215.
4) Abe S, Suzuki T, Ito T, *et al*: Effects of single and repeated phencyclidine administration on the expression of metabotropic glutamate receptor subtype mRNA in rat brain. Neuropsychopharmacology, 2001; 25: 173–184.
5) Yamaguchi M, Suzuki T, Abe S, *et al*: Repeated cocaine administration differentially affects NMDA receptor subunit (NR1, NR2A–C) mRNAs in rat brain. Synapse, 2002; 46: 157–169.
6) Suzuki T, Koizumi J, Shiraishi H, *et al*: Psychiatric disturbance in mitochondrial encephalopathy. J Neurol Neurosurg Psychiatry, 1989; 52: 920–922.
7) Kurita H, Maeshima H, Kida S, *et al*: Serum dehydroepiandrosterone (DHEA) and DHEA-sulfate (S) levels in medicated patients with major depressive disorder compared with controls. J Affect Disord, 2013; 146: 205–212.
8) The Japanese Society of Psychiatry and Neurology and the Japan Society of Obstetrics and Gynecology: Clinical guide for women with mental health problems during the perinatal period: Overview. https://www.jspn.or.jp/uploads/uploads/files/activity/Clinical_guide_for_women_with_mental_health_problems_during_perinatal_period_ver1.2.pdf (Accessed May 31, 2023) (in Japanese)
9) The Japanese Society of Psychiatry and Neurology and the Japan Society of Obstetrics and Gynecology: Clinical guide for women with mental health problems during the perinatal period: Detailed Contents. https://www.jspn.or.jp/uploads/uploads/files/activity/Clinical_guide_for_women_with_mental_health_problems_during_perinatal_period_details_ver1.2.pdf (Accessed May 31, 2023) (in Japanese)
10) Kinjo T, Ito M, Seki T, *et al*: Prenatal exposure to valproic acid is associated with altered neurocognitive function and neurogenesis in the dentate gyrus of male offspring rats. Brain Res, 2019; 1723: 146403.

Perspectives

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My 40-year Career as a Hematologist – Facing Clinical Challenges and Changing My Research – Focus from Glycolipids to Therapy Resistance –

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It has been about 40 years since I graduated from Juntendo University School of Medicine in 1983. For 5 years after graduation, I was engaged in research on glycolipids in the Biochemistry Unit of the University of Tokyo. Later, I wrote and published papers on glycolipids. Eventually, I began to work here at the Department of Hematology. In 2000, in the 17th year after my graduation, I began to work at the Department of Hematology, Juntendo University Urayasu Hospital, as the only physician stationed there. I had to work long hours, until late night, to manage the many inpat As described in our department's homepage, 145 (64%) of the 227 presentations made at professional society meetings were made by residents. During this period, 15 new residents joined this department. In 2015, contributions by residents were accepted for publication by high-impact-factor journals, such as the Journal of Clinical Oncology. With the support of our Chairman Ogawa, in April 2023, I began to work as a specially appointed professor at the current department. Recently, I have begun to feel deeply grateful for Juntendo university's academic motto of "Benevolence," its principle of "Uninterrupted Advancing," and its academic position of "three noes principle, *Sanmu* Principle (no discrimination based on gender, nationality, or academic background)". I hope that you will all remain active under these principles and ideas, while taking due care of your own health. I wish to express my appreciation for your continued support and cooperation.

Key words: glycolipid, resident-centered professional society presentation, hematopoietic tumor, mechanism for therapy resistance

Preface

I am pleased to announce that I will be retiring at the end of March 2023. I would like to express my sincere gratitude to Chairman Hideoki Ogawa and the many others who have guided and supported me throughout the years.

Before Urayasu Hospital

I graduated in 1983, about 40 years ago, from Juntendo University School of Medicine. During the first 5 years after graduation, I worked at the Department of Collagen Disease and Rheumatology. In those days, close attention was being paid to research on serum phospholipid autoantibodies in patients with systemic lupus erythematosus (SLE). Under such circumstances, I began to engage in research on glycolipids under the guidance of Associate Professor Iwamori (Second Department of Biochemistry, School of Medicine, University of Tokyo). My research was later focused on antigen epitopes recognizing autoantibodies to glycolipids rather than phospholipid autoantibodies, and I published several papers (Figures 1–4). All of these

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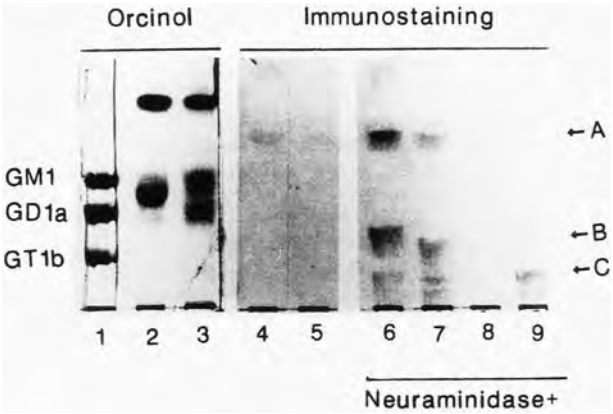

Figure 1 TLC immunostaining of intact and neuramini dase-treated gangliosides from spleens (BALB/c and NZB mice) stained with sera from NZB mice, followed with peroxidase-conjugated goat anti-mouse lgM antibody[1)]
The bands were stained with orcinol-H2S04 reagent (lanes l to 3), and by TLC-immunostaining without (lanes 4 and 5) and with neuraminidase treatment (lanes 6 to 9) of the TLC plates. Standard gangliosides, GMl, GDla, and GT1b (lane l), gangliosides from fresh weight 100 mg of BALB/c mouse spleens (lanes 3,5 and 9) and NZB mouse spleens (lanes 2,4 and 6), monosialogangliosides (lane 7) and di plus trisialogangliosides (lane 8) from fresh weight 100 mg of NZB mouse spleens were spotted on the plates, respectively. At least, three monosialogangliosides A,B, and C (shown by arrows) from NZB mouse spleens as well as BALB/c mouse spleens were reacted with lgM autoantibodies in sera from NZB mice only after neuraminidase treatment (lanes 6,7, and 9).

studies were based on analyses using thin-layer chromatography and immunostaining.

Figure. 1 shows the antigen-recognizing site of autoantibodies from NZB mice (a model of SLE being studied by Prof. Shirai, Second Department of Pathology) explored by immunostaining on thin-layer chromatograms. Orcinol staining indicates the control position. Neuraminidase is an enzyme that digests the sialic acid at the sugar chain terminal[1)].

In 1990, I received my PhD degree in medicine. My doctoral thesis was entitled "Analysis of Anti-lymphocyte Antibodies and Corresponding Glycolipid Antigens in Blood of Patients with Systemic Lupus Erythematosus by Means of TB Cell Lines and Cellular Enzyme Antibody Technique." As shown in Figure 2, an anti-lymphocyte antibody was detected in the blood of patients with SLE, and the antigen-recognizing site of this antibody was shown to be glycolipids, including at least 3 types of sialic acid. The presence of these glycolipids, accompanied by hypocomplementemia, seemed to be responsible for the lymphopenia in SLE[2)].

Figure 3 and Table 1 illustrates that in mouse fetuses, the thymus lymphocytes show gradual extension of the sugar chain of the cell surface glycolipids, as these lymphocytes undergo differentiation during the course of intrauterine develop-

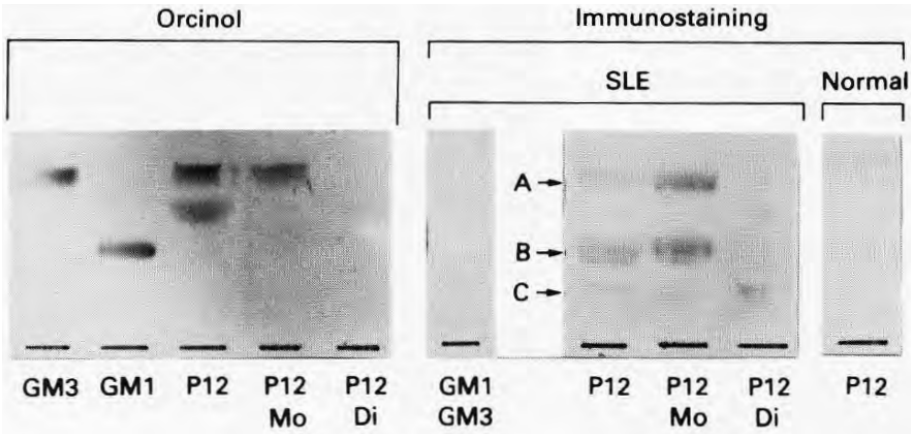

Figure 2 Thin layer chromatography immunostaining of acidic glycosphingolipids[2)]
From P12 cells with serum samples from a patient with SLE and a normal control subject.
The acidic glycosphingolipids from P12 cells are abbreviated to P12. The monosialo- and disialo glycosphingolipids from P12 cells abbreviated to P12Mo and P12Di, respectively. The left hand plate was stained with orcino-H2SO4 reagent. The right hand plate was immunostained with a serum sample containing the highest detected titer of IgG antibodies to P12 and a normal control. Monosialogsphingolipids A, B, and C were stained by serum samples from the patient but not the normal control subjects.

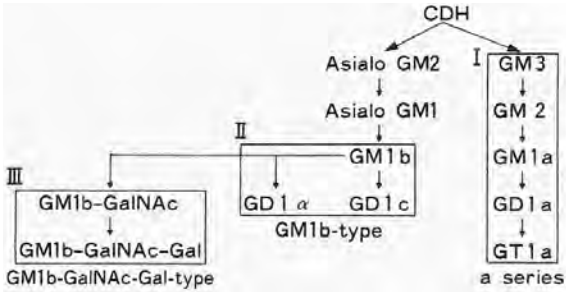

Figure 3 Ganglioside synthetic pathways during T cell developecnt in mice[3)]

Gangliosides are produced by the sequential addition of sugars to ceramide dihexosides (CDH). Three ganglioside synthetic pathways (I, H, and III) are used during T cell development in micc: I, (a series) CDH plus NeuAc or NeuGc (neuramic acid, GM3), GM3 plus N-acctylgalactosamine (GM2), and GM2 plus galactose (GMla); II, (GMlb- type). CDH plus NeuAc_acctylgalactosamine (asialo GM2), asialo GM2 plus galactose (asialo GMl), and asialo GM 1 plus neuramic acid (one; GMlb, two; GMl*a*, or GMlc and III, (GMlb-GalNAc-Cal-type).

ment[3)].

Figure 4 illustrates that the anti-GM1 and anti-GD1b antibodies in the blood of a patient with B-cell lymphoma induced multiple peripheral neuritis through reactions with the peripheral nerve myelin sheath. This seemed to play a significant etiological role[4)].

To expand my clinical knowledge and skills, I also worked at the Tokyo Metropolitan Matsuzawa Hospital, the Koshigaya Municipal Hospital, etc. Then, I began to work at the Department of Hematology. Moving from such departments to the department of hematology seems to be a rare career choice for physicians. I also worked at the departments of hematology, etc., at the Shizuoka Hospital, Kameda Medical Center, etc., for the purpose of clinical training.

After Urayasu Hospital

In 2000, in the 17th year after my graduation, I began to work at the Department of Hematology, Juntendo University Urayasu Hospital, as the only physician stationed there. The number of patients visiting my office increased gradually, and I became rather busy. Before long, the number of inpatients at this department increased to about 30, and I had to work long hours, until late night, to manage the many inpatients as well as outpatients. I was often called at night and also on weekends or holidays, including while I was bathing or asleep, to manage sudden changes in the conditions of patients. After about two years, another physician was sent to this department as a rotation staff member from the medical office. In 2007, I was appointed as a Senior Clinical Associate Professor at the Department of Hematology, Juntendo University Urayasu Hospital. The number of physicians working at this department then increased gradually, and many residents and physicians working here began actively committing themselves to making presentations at professional society meetings and writing papers in English for publication.

In 2013, I was appointed as Professor at the Department of Hematology, Juntendo Urayasu Hospital. As described in our department's home-

Table 1 Summary of T Cell Surface Markers during Ontogency in Mice[3)]

	Days of gestation			
Surface markers	13-14	14-15	15-17	17 days to 4 weeks
GM1a (a series)	±	+	±	−
GMlb-type	±	+	+	−
GM1b-GalNAc-Gal	−	−	±	+
Asialo GMI	−	±	±	±
Thy-1	±	+	+	±
TCR ($\gamma\delta$)	±	+	−	−
IL-2R	−	+	−	−
CD4	−	−	+	±
CD8	−	−	+	±
TCR ($\alpha\beta$)	−	−	±	+

Note. +, increased; ±, slightly changed; −, decreased.

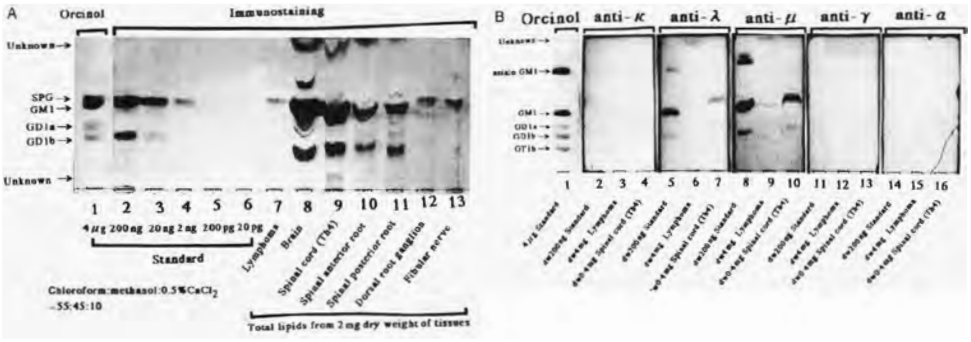

Figure 4 Thin-layer chromatography (TLC) immunostaining of an extract from the patient's neural tissues stained with patient serum IgM λ antibody in the patient's serum preferentially bound glycolipids GM1 and GD1b[4].
(A) TLC immunostaining with serum followed by anti-IgM antibody (lanes 2-13): lanes 1-6, purified glycolipid mixture as a standard [sialylparagloboside (SPG), GM1, GD1a and GD1b]; lane 7. lipids from the patient's lymphoma cells; lane 8, brain; lane 9, spinal cord (Th4); lane 10, spinal anterior root; lane 11, spinal posterior roots; lane 12, spinal dorsal root ganglion: lane 13, fibular (common peroneal) nerve.
(B) TLC immunostaining with serum followed by anti-human immunoglobulin antibodies: anti-κ light chain (lanes 2-4), anti-λ light chain (lanes 5-7), anti- μ heavy chain (lanes 8-10), anti- γ heavy chain (lanes 11-13) and anti-α heavy chain (lanes 14-16).

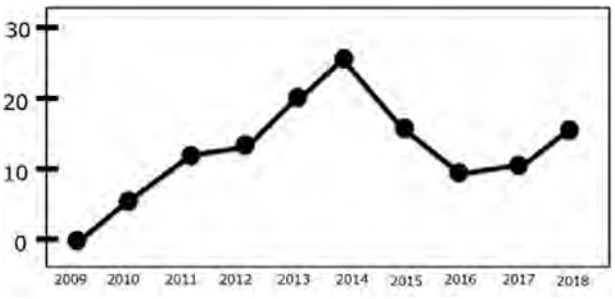

Figure 5 Annual conference presentations by Urayasu Hospital hematology interns
Home page URL: https://www.hosp-urayasu.juntendo.ac.jp/medicalcare/hematology/[5]

page which we further enriched, 145 (64%) of the 227 presentations made at professional society meetings were by residents. During this period, 15 new residents joined our department. Figure 5 shows the annual number of presentations made at professional society meetings by the residents of Urayasu Hospital. The number is large and I served as a guide to many of these residents when they made presentations of diverse cases[5].

Figure 6 and Table 2 shows a very rare case encountered at our hospital. The paper on this case was accepted for publication in the Journal of Clinical Oncology, which has a high-impact-factor.

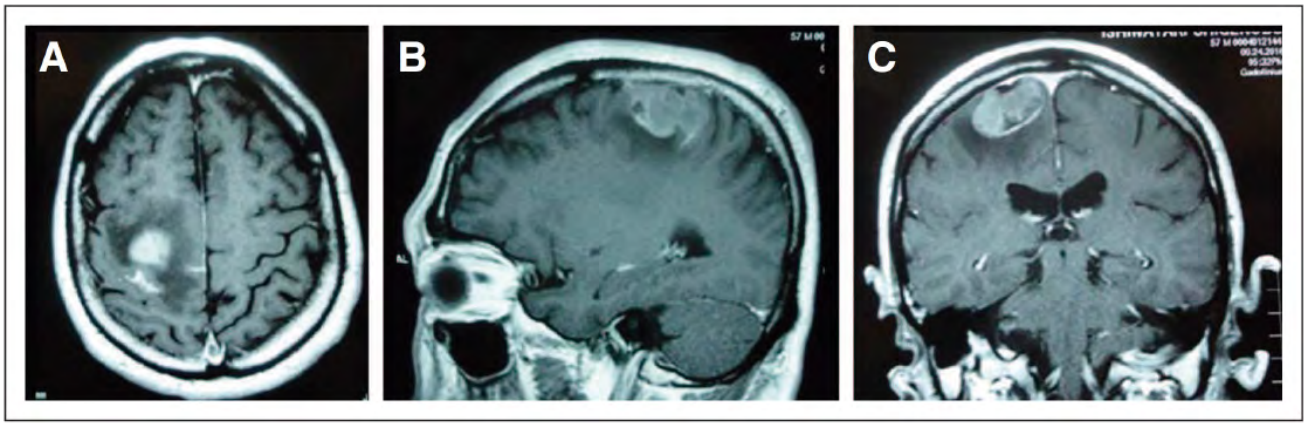

Figure 6 A brain magnetic resonance imaging examination (T1-weighted image) revealed a tumorous lesion (30 x 30 mm) showing a homogeneous and intense gadolinium enhancement in the right frontal to parietal lobe, surrounded by edema. Bleeding inside the tumor was also (Figure 6A, noted, axial; Figure 6B, sagittal; Figure 6C, coronal)[6]

Table 2 Summary of primary CNS mantle-cell lymphomas in the literature[6)]

Patient	Age (Years)	Sex	Location	Markers	IPI	PCNSL IPI	Treatment	Outcome	Reference
1	74	F	Frontoparietal region/CSF	$CD5^+$ $CD20^+$ $CD10^-$ $CD23^-$	LI*	High	MTX	Dead, 1 month	4
2	29	M	CSF	$CD5^+$ $CD20^+$ lgG^+	Low*	Low*	ASCT	CR	5
3	55	M	Frontal lobe/ CSF	$CD5^+$ $CD20^+$ $CD10^+$ $CCND1^+$	Low	Low	MTX,Ara-C	Dead, 4 months	Current article

Abbreviations: Ara-C, cytarabine; ASCT, autologous stem-cell transplantation; CCNDl, cyclin D1;CR, complete remission; lgG, immunoglobulin G; IPI, International Prognostic Index; LI, low intermediate; MTX, methotrexate; PCNSL, primary CNS lymphoma.
*Concerning.

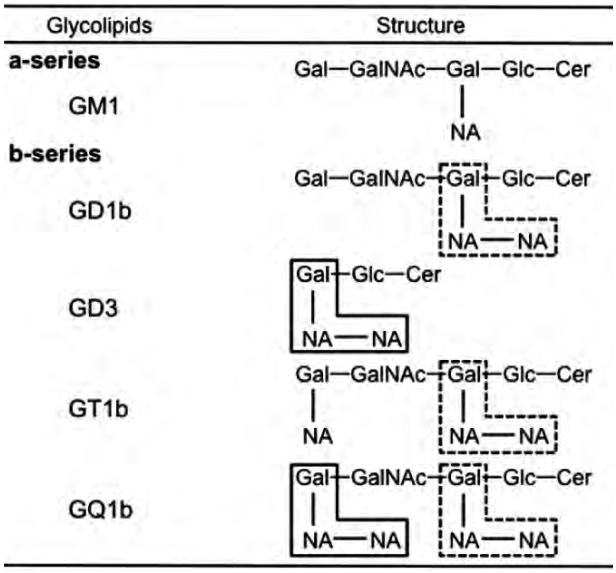

Figure 7 Structures of GM1, GD1b, GD3, GT1b, and GQ1b gangliosides[7)]
Structures of GM1, GD1b, GD3, GT1b, and GQ1b gangliosides. Three terminal residues of NeuNAc(*α*2-8) NeuNAc(*α*2-3) Gal in GD3 and GQ1b gangliosides (solid lines) and three internally located terminal residues of NeuNAc(*α*2-8) NeuNAc(*α*2-3) Gal residue in GD1b, GT1b, and GQ1b gangliosides (dotted lines) are shown.

This was a case of double hit mantle cell lymphoma of the central nervous system[6)].

Figure 7 demonstrates that the anti-glycolipid antibody in the blood of patients with mantle cell lymphoma reacted with the peripheral motor nerves. This seemed to be a significant etiological factor[7)].

Table 3 illustrates our finding that malignant lymphoma itself produces cytokines (TGFbeta1, TNFalpha) and thereby induces fibrosis. This seemed to serve as a significant etiological factor[8)].

Around 2018, I began to study the mechanisms of resistance of hematopoietic tumors to treatment. At present, I am submitting a paper on therapy resistance of large B-cell lymphoma (Figure 8). The new histological prognostic index is important for predicting the responses of large B-cell lymphoma to treatment. Prediction of the treatment response involves 6 factors (GRP94, CYP3A4, AKR1C3, MDR1 and MRP1 P53)[9)].

Thanks to our Chairman Ogawa, in April 2023, I began to work as a specially appointed professor at the current department (Department of Hematology, Juntendo University Urayasu Hospital). From now on, I plan to work actively to extend cooperation for the attempts of residents and other medical members of our department to make presentations, publish papers, etc., about their research.

Recently, I have begun to feel deeply grateful for Juntendo university's academic motto of "Benevolence," its principle of "Uninterrupted Advancing," and its academic position of "three noes principle, *Sanmu* Principle (no discrimination based on gender, nationality, or academic background)." I hope that you will all remain active under these principles and ideas, while taking due care of your own health. I wish to express my appreciation for your continued support and cooperation.

Acknowledgments

I would like to thank all of the team members who have worked at the Department of Hematology in Urayasu Hospital over the 20 years, supporting a large number of activities.

Funding

No funding was received.

Table 3 Evaluation of the odds ratios for fibrosis associated with positive immunostaining regarding TGF-beta1, TNF-alpha1, and combination of TGF and TNF[8)]

	n	Fibrosis vs TGF		Fibrosis vs TNF		Fibrosis vs TGF+TNF	
		Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value	Odds Ratio (95%CI)	p-value
All tissue	104	12.80 (4.94-33.20)	< 0.001**	1.75 (0.79-3.90)	0.171	3.35 (1.87-6.00)	< 0.001**
Bone marrows	27	13.70 (2.05-92.00)	0.007**	2.75 (0.55-13.70)	0.218	4.60 (1.31-16.1)	0.017*
AML	7	–	–	–	–	1.00 (0.11-8.75)	1.000
ALL	7	–	–	–	–	–	–
DLBCL	40	12.80 (2.48-66.00)	0.002**	2.04 (0.52-8.00)	0.308	4.45 (1.43-13.80)	0.010*
FL	11	3.50 (0.15-84.70)	0.441	1.25 (0.06-26.90)	0.887	1.54 (0.27-8.69)	0.626
T-cell lymphoma	8	–	–	0.50 (0.02-12.90)	0.676	2.51 (0.23-27.40)	0.451
Others	14	–	–	1.33 (0.14-12.80)	0.803	3.91 (0.79-19.30)	0.094

Notes:
CI, confidence interval
Odds ratios are relatively accuracy in fibrosis of all disease vs TGF betal, especially in DLBCL.

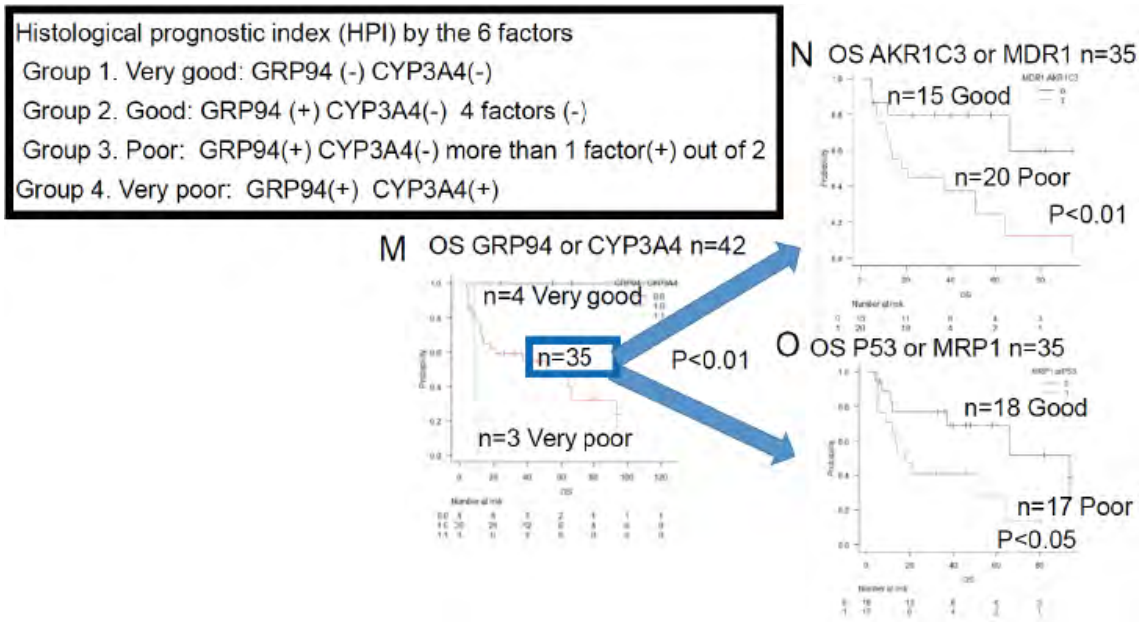

Figure 8 Overall survival of large B-cell lymphoma patients with and without the prognostic factors Kaplan-Meier survival curves and between-group comparisons[9)]
M. GRP94- CYP3A4- n = 4 Group1 Very good (5-year OS 100%)
GRP94+ CYP3A4- n = 35
In the Group 4 (Very poor, n = 3) consisting of 3 patients with positivity for both GRP94 and CYP3A4. All the 3 patients died within a short period. $p < 0.01$
N. AKR1C3- or MDR1- negative n = 15, positive n = 20, $p < 0.01$
O. P53 or MRP1 negative n = 18, positive n = 17, $p < 0.05$
Group 1 (n = 4), the "Very good" group, consisted of 4 patients who showed negative staining for both GRP94 and CYP3A4, including 2 patients who were censored. This group had an extremely good prognosis, and all the 4 patients survived (5-year OS: 100%). On the contrary, Group 4 (n = 3), the "very poor" group, consisted of 3 patients who showed positive staining for both GRP94 and CYP3A4. This group had a very poor prognosis and all the 3 patients died within a short period of time. The prognosis of patients in the Group 2 and 3 (n = 35) was intermediate, with the median survival of about 51 months. In Figure 1N and O, the intermediate prognosis group, that is, Group 2 (n = 35), is subdivided into "Group 2 (Good)," consisting of patients who showed negative staining for both AKR1C3 and MDR1, and "Group 2 (Good)" consisting of patients who showed negative staining for both p53 and MRP1. The remaining of Group 3 had a poor prognosis.

Author contributions

MN wrote, read and approved the final manuscript.

Conflicts of interest statement

A Conflict of Interest statement is not included for each of the authors.

Author has no conflicts of interest.

References

1) Noguchi M, Iwamori M, Hirano T, *et al*: Preferential reactivity of autoantibodies in murine lupus NZB mice to neuraminidase-treated monosialogangliosides on B cells of mouse spleen. Cellular Immunol, 1991; 135: 184-194.
2) Noguchi M, Iwamori M, Hirano T, *et al*: Autoantibodies to T and B cell lines detected in serum samples from patients with systemic lupus erythematosus with lymphopenia and hypocomplementaemia. Ann Rheum Dis, 1992; 51: 713-716.
3) Noguchi M, Suping Z, Taguchi J, *et al*: Unique T cell differentiation markers: gangliosides with cholera toxin receptor activity on murine fetal thymocytes. Cellular Immunol, 1994; 156: 402-413.
4) Noguchi M, Mori K, Yamazaki S, Suda K, Sato N, Oshimi K: Multifocal motor neuropathy caused by a B-cell lymphoma producing a monoclonal IgM autoantibody against peripheral nerve myelin glycolipids GM1 and GD1b. British Journal of Haematology, 2003; 123: 600-605.
5) Annual conference presentations by Urayasu Hospital hematology interns. https://www.hosp-urayasu.juntendo.ac.jp/medicalcare/hematology/ (Accessed Jan. 6, 2023) (in Japanese)
6) Sakurai H, Sugimoto S, Shimada A, *et al*: Primary CNS CCND1/MYC-Positive Double-HitB-Cell Lymphoma: A Case Report and Review of the Literature. J Clin Oncol, 2015; 33: e79-83.
7) Mori A, Ueno Y, Shimura H, *et al*: Motor-dominant polyneuropathy due to IgM monoclonal antibody against disialosyl gangliosides in a patient with mantle cell lymphoma. J Neurol Sci, 2014; 337: 215-218.
8) Takizawa H, Araki Y, Fujishiro M, *et al*: Role of TGF-beta1 and TNF-alpha1 produced by neoplastic cells in the pathogenesis of fibrosis in patients with hematologic neoplasms. J Clin Exp Hematop, 2023; 63: 83-89.
9) Nitta H, Takizawa H, Mitsumori T, *et al*: Possible New Histological Prognostic Index for large B-cell lymphoma. Journal of Clinical Medicine, under review.

Original Articles

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2023. 69(4), 300–306

Oligodendrocyte Cell Line OLP6 Successfully Differentiates on Decellularized Brain Tissue

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Objectives: The mechanisms of mental and neurological diseases have been proposed to be related not only to disorders of the neurons but also to the environment surrounding neurons, such as glial cells and the extracellular matrix (ECM). The chondroitin sulfate (CS) chain, which comprises CS proteoglycans (CSPGs), is one of the major sulfated glycosaminoglycans in the brain. CSPGs play an important role in the development, aging, and pathological conditions of the central nervous system. In particular, CSPGs play critical roles in oligodendrocyte differentiation and cell activity. Conventional two-dimensional culture in a glass chamber hardly replicates the complexity of the ECM structure or mimics *in vivo* conditions. Therefore, to solve this issue, this study aimed to use a culture system with decellularized tissue as a scaffold of organized ECM, thereby enabling the observation of cell differentiation and interactions between cells and the surrounding ECM.
Materials and Methods: We investigated the differentiation potential of the OLP6 cell line using decellularized brain tissue as the substrate.
Results: We observed that OLP6 differentiated faster on decellularized brain tissues than on conventional 2D-coated surfaces. The relative mRNA expression levels of *CNP*, *PNP*, and *MBP* as well as CSPGs were increased under 3D culture conditions.
Conclusions: Our study provides the first evidence of the advantages of cell culture on decellularized tissues for the investigation of oligodendrocyte differentiation and cell/ECM interactions.

Key words: oligodendrocyte, cell culture, decellularized brain tissue

Introduction

In recent years, the pathological mechanisms of psychiatric and neurological disorders have been suggested to be related not only to neuronal defects but also to the environment surrounding neurons, such as glial cells, oligodendrocytes, and extracellular matrix (ECM). Oligodendrocytes, a glial cell type, form myelin sheaths in the central nervous system (CNS), and their main function is to induce saltatory conduction and increase the conduction rate of action potentials. In addition, oligodendrocytes that do not form myelin have been shown to contact neurons and play a variety of roles in neuronal signaling[1, 2].

Several oligodendrocyte cell lines have been established using human oligodendrocytes[3], rat oligodendrocytes[4], and mouse oligodendrocytes[5]. In this study, we used the OLP6 cell line derived from adult rat oligodendrocytes[6]. This immortalized oligodendrocyte cell line harbors the temperature-sensitive Simian virus 40 large T-antigen gene, which allows the differentiation of oligodendrocytes in a timely manner when the culture

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temperature is increased from 33 °C to 39 °C. In recent years, the importance of the interaction between oligodendrocytes and ECM has been highlighted, in addition to the relationship between oligodendrocytes and neurons, *in vivo*. For example, chondroitin sulfate proteoglycan (CSPG), one of the components of the ECM, is produced by oligodendrocyte precursor cells (OPCs), and their chondroitin sulfate glycosaminoglycans (CS-GAGs) have been reported to inhibit oligodendrocyte differentiation[7]. Thus, the relationship between oligodendrocytes and the ECM is of research interest to clarify the pathology of mental and nervous disorders. CSPGs have also been shown to inhibit OPC process outgrowth and differentiation *in vitro*[8]. Currently, a 2D culture method using dishes has been established for culturing oligodendrocytes, and ECM molecules, such as laminin, fibronectin, and Matrigel, have been used as surface coatings to study their effects on oligodendrocyte primary culture[9]. However, such 2D cultures fail to replicate the complexity of the ECM structure that exists in living organisms; therefore, it is not an appropriate tool to reproduce living organisms three-dimensionally and to observe the relationship between oligodendrocytes and the ECM. In addition, it was recently proposed that ECM stiffness plays a critical role in OPC activity[10]. Thus, the complexity of ECM composition and structure cannot be investigated in a 2D culture setup.

Decellularization of tissues to obtain ECM with native composition and mechanical properties has recently been used to study the role of the ECM in stem cell differentiation[11, 12]. Therefore, the present study aimed to present a protocol for brain tissue decellularization, in which only cellular components are removed from the tissue, and establish a 3D culture system for oligodendrocytes using the decellularized brain tissue as a substrate to culture oligodendrocytes in a three-dimensional environment that is closer to the *in vivo* conditions than conventional artificial culture substrates.

Materials and Methods

Animals

Eight ten-week-old C57BL/6J male mice, purchased from Jackson Laboratory, were used to create the decellularized brain tissue. All animal protocols were approved by the Animal Care and Use Committee of Juntendo University.

Cell line

The OLP6 cell line (Neuroscience 2005; 136: 115-121) was obtained from the Riken Cell Bank (Cell No. RCB2864) and was grafted on the decellularized brain tissue.

Decellularization

The procedure for mouse brain section decellularization was modified from that reported by De Waele et al. (2015). Mice were perfused with 25 mL of ice-cold phosphate-buffered saline (PBS) containing 1% heparin. The brains were dissected, and 500 μm-thick coronal sections of the brain (between bregma 1 and bregma -1.5 mm) were obtained using a vibratome (VT1200S; Leica, Weltzar, Germany). The sections were first placed in demineralized water (dH_2O) for 10 min and then incubated in dH_2O containing 4% sodium deoxycholate (Fujifilm Wako Pure Chemical Industries Ltd., Tokyo, Japan). After washing with PBS, the sections were placed in dH_2O and 5% Triton X-100 (Nacalai Tesque Inc., Kyoto, Japan), followed by another wash with PBS. This incubation sequence was repeated three times. Finally, DNA was eliminated by incubating the sections with 40 kU/mL DNaseI (D4263; Sigma-Aldrich, St. Louis, MO, USA) diluted in 1M NaCl during the last cycle. The decellularized brain tissues were stored at 4°C in PBS containing 2% penicillin/streptomycin (cat. 15140122; Gibco™, Thermo Fisher Scientific, Waltham, MA, USA) and 0.8% amphotericin B. All incubations were at room temperature in a sterile environment in 24-well plates placed on a rotary shaker (NA-301N; Nisshin Rika Co., Ltd., Tokyo, Japan) at 100 rpm.

2D and 3D Cultures

OLP6 was maintained in culture buffer containing neurobasal medium (cat. 21103049; Gibco™) supplemented with 5% fetal bovine serum, B27 supplement (cat. 17504044; Gibco™), 0.5 mM glutamine (cat. 25030081, Gibco™), 20 ng/mL epidermal growth factor (EGF; 100-15; Peprotech, Thermo Fisher Scientific), fibroblast growth factor (FGF)-2 (100-18C; Peprotech), and 1% penicillin/streptomycin (cat. 15140122; Gibco™). The cell line was cultured under 5% CO_2 at 33°C for proliferation and 39°C for differentiation. 2D and 3D cultures were performed according to the schedule shown in Figure 1. The

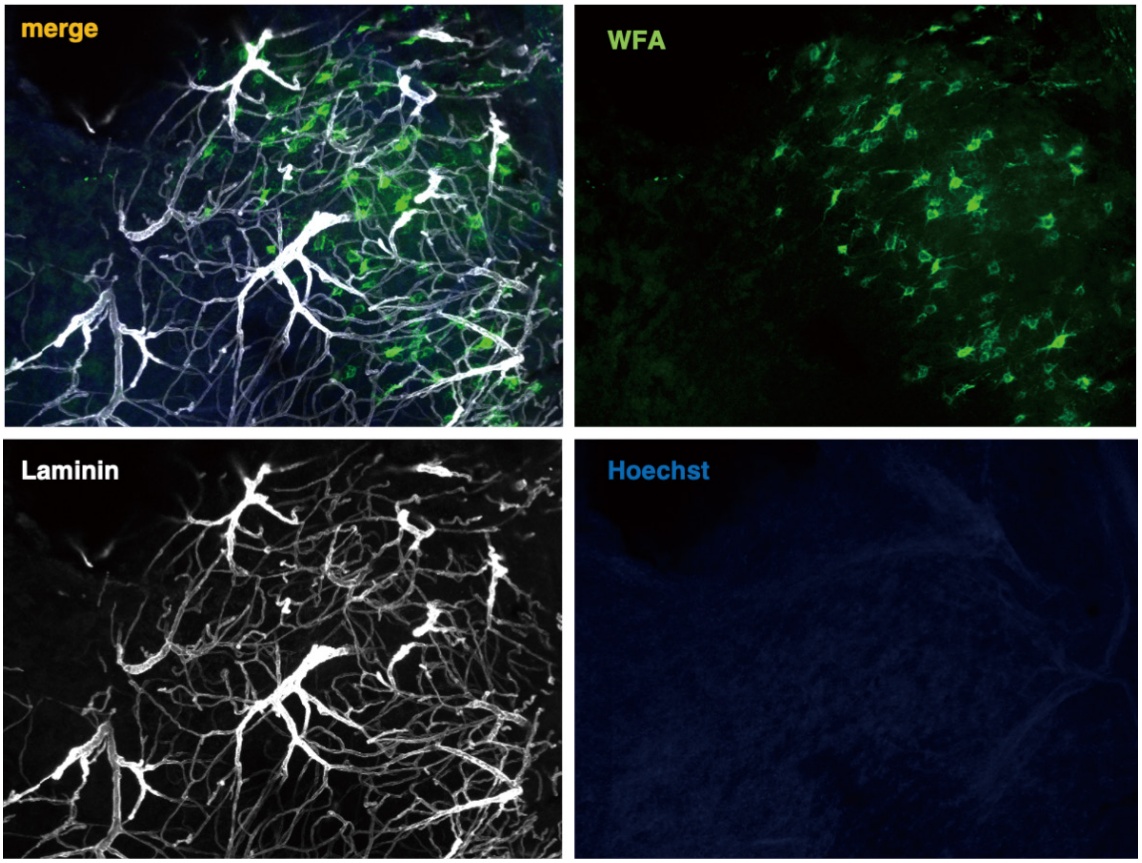

Figure 1 Confocal image of the decellularized brain tissue stained with laminin (white), Wisteria floribunda lectin (WFA) (green), and the nuclear marker Hoechst (blue).

cell proliferation period was 48 h. The medium was changed once every two days. In both the 2D and 3D samples, the time point for observation and analysis was set at 24 h from the start of differentiation.

2D culture

OLP6 cells were cultured on 100 mm collagen I-coated dishes (cat. 4020-010; Iwaki, AGC Techno Glass Co. Ltd., Yoshida, Japan) at 33°C until confluence was achieved. For 2D culture observation, 500 μL of a medium at a density of 5×10^5 cells was placed in each well of a Collagen I 8-well Culture Slide (cat. 354630; Corning BioCoat, Glendale, AZ, USA) and subjected to immunostaining.

Graft on the decellularized brain tissue for 3D culture

The decellularized brain tissue was rinsed in a chondroitinase buffer (50 mM Tris-HCl, 60 mM sodium acetate, 0.02% bovine serum albumin, pH = 8.0) containing 200 mU/mL chondroitinase ABC (C3667; Sigma-Aldrich) for 2 h at 37°C in to decompose and remove the chondroitin sulfate chains before the graft and then washed with PBS containing 2% penicillin/streptomycin and 0.8% amphotericin B. For the graft, 40 μL of a medium at a density of 2×10^5 cells was poured onto half of the brain tissue. All animal experiments followed the Fundamental Guidelines for Proper Conduct of Animal Experiments and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology (Notice No. 71, 2006) and were approved by the Committee for Animal Experimentation at Juntendo University (Approval No. 2022300).

Immunohistochemistry

Samples were fixed in cold 4% paraformaldehyde (in PBS) for 20 min and washed with PBS. The samples were then placed in 0.5% Triton X-100/PBS solution for 15 min, followed by 15 min incubation in blocking solution (0.2% gelatin/PBS). Each antibody, diluted at a ratio of 1:400 in blocking solution (0.2% gelatin/PBS), was applied to the samples

overnight at 4°C and then washed with PBS. The following primary antibodies and markers were used: laminin (rabbit polyclonal; Cat#L9393; 1:1000; Sigma-Aldrich), sox10 (rabbit monoclonal IgG; Cat# 11570; 1:1000; Abcam, Cambridge, UK), CNPase (mouse monoclonal IgG1; MAB326; 1:200; Merck KGaA, Darmstadt, Germany), Wisteria floribunda lectin (biotinylated; Cat#L1516; 1:800; Sigma-Aldric), Phalloidin-alexa488 (Cat# 11570; 1:400; Thermo Fisher Scientific). The sections were then rinsed, and secondary antibodies were applied for 60 min at 25°C. The secondary antibodies used were goat anti-rabbit Alexa Fluor-647, goat anti-mouse IgG1 Alexa Fluor-546, and streptavidin Alexa Fluor 488 (1:400 dilution in PBS; Thermo Fisher Scientific). After immunostaining, the cultured samples were incubated with nuclear dye (1 μL/mL in PBS; Hoechst, H3570; Thermo Fisher Scientific) for 20 min at 25°C. After extensive washing in PBS, the sections were mounted on a fluorogel with Tris buffer (Electron Microscopy Sciences, Hatfield, PA, USA). Imaging was performed within 24 h on an LSM780 microscope (Zeiss, Jena, Germany).

Quantitative real-time PCR

RNA cell lysates were extracted using the Rneasy Mini Kit (Qiagen, Valencia, CA, USA). cDNA was synthesized using the RT2 First strand (#330404; Qiagen). Real-time PCR was performed using Fast SYBR Green Master Mix (#4385612; Applied Biosystems) on a Fast 7500 Real-Time Cycler (Applied Biosystems, Foster City, CA, USA). The gene GAPDH was used as an endogenous control. The primers used are listed in Table 1.

Statistical analysis

Statistical analysis was performed using PRISM statistical software (Prism 9, GraphPad Software, San Diego, CA, USA). Data are presented as mean ± standard error of the mean. Unpaired *t*-test or analysis of variance (ANOVA) with Tukey's multiple comparison test were performed.

Results

ECM structures are preserved after tissue decellularization

We first confirmed the removal of cell components and the condition of the ECM after decellularization. Hoechst staining of the decellularized tissue showed that all nuclear contents were cleared, while laminin immunostaining showed that the vascular basement membrane remained intact. In addition, Wisteria floribunda lectin staining showed that even fine ECM structures, such as perineuronal nets, were intact after the decellularization process (Figure 1).

Differentiation of OLP6 in 2D and 3D cultures

To compare the differentiation of oligodendrocytes in 2D and 3D cultures, we cultivated OLP6 cells under differentiation conditions for 24 h (39 °C, with serum, EGF, and FGF-2). A significantly higher proportion of sox10-positive cells also expressed the mature oligodendrocyte marker CNPase in the 3D culture (1.325 ± 0.1702% in 2D; 18.37 ± 0.1568% in 3D; $p < 0.0001$, unpaired *t*-test; Figure 2A-C). In addition, the RNA expression levels of the mature oligodendrocyte markers *CNP*, *PLP*, and *MBP*, were not significantly increased after differentiation for 24 h under 2D conditions (Figure 2D-F). However, the relative expression levels of *CNP*, *PNP*, and *MBP* on day 1 under 3D culture conditions increased by 3.5-fold (adjusted $p = 0.0002$, ANOVA with Tukey's multiple comparison tests; Figure 2D), 5.2-fold (adjusted $p = 0.0002$, ANOVA with Tukey's multiple comparison tests;

Table 1 List of primers used for quantitative real-time PCR

Gene	Forward primer	Reverse primer
GAPDH	ACTCTACCCACGGCAAGTTC	GATGGTGATGGGTTTCCCGT
CNPase	TTTGCCCGAAAAAGCCACACA	CACCGTGTCCTCATCTTGAAG
MBP	ACACAAGAACTACCCACTACGGC	CCAGCTAAATCTGCTGAGGGA
PLP	CCAGAATGTATGGTGTTCTCCC	GGCCCATGAGTTTAAGGACG
Tenascin-R	TCATCTCCATTACTGCTGAGAGG	AGTGCAAGTGGGAGATAGGG
Phosphacan	AACCATCCTTGGAAAACACG	CATTGGTGAGATTTATTTCCACTGT
Brevican	AGCAGAACCGCTTCAATGTC	TCAGAGGAAGCAGAGGGATG

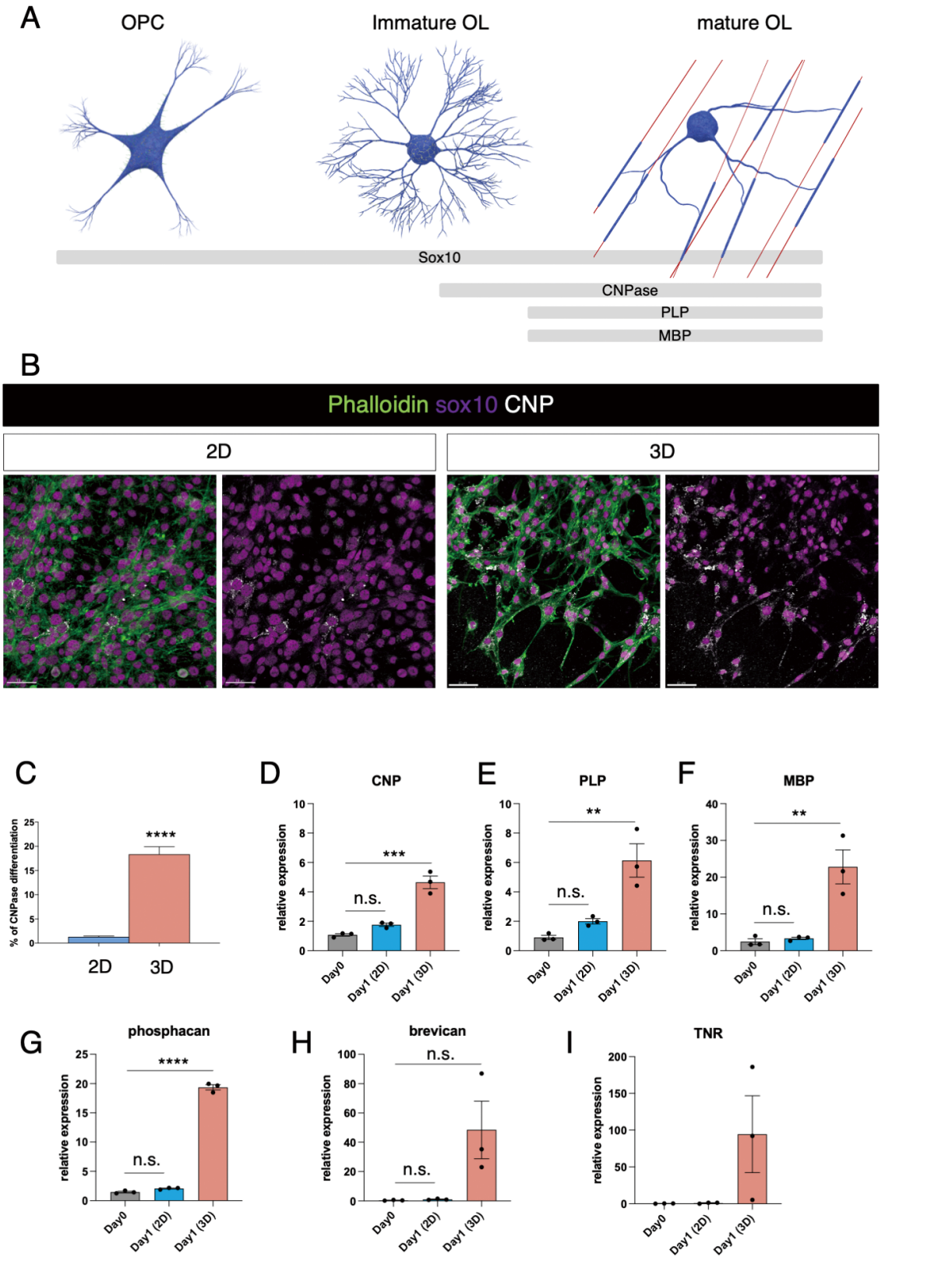

Figure 2 A. Schematic depiction of oligodendrocyte lineage and associated markers. B. Confocal images of OLP6 under 2D and 3D culture conditions after a 24-h differentiation period. C. Bar graph displays the ratio of sox10-positive cells that also expressed CNPase after 24 h of differentiation under 2D and 3D culture conditions. D–F. Bar graphs display the relative expression of oligodendrocyte differentiation markers on day 0 and after 24 h of differentiation under 2D and 3D culture conditions. (*** $p = 0.0002$; ** $p = 0.0035$ in E and 0.0045 in F, ANOVA with Tukey's multiple comparison test). G–I. Bar graphs display the relative expression of chondroitin sulfate proteoglycans *phosphacan*, *brevican*, and *tenascin-R* on day 0 and after 24 h of differentiation under 2D and 3D culture conditions. (**** $p < 0.0001$, ANOVA with Tukey's multiple comparison test).

Figure 2E), and 13-fold (adjusted p = 0.0045, ANOVA with Tukey's multiple comparison tests; Figure 2F), respectively, compared those on day 0. We also observed that the expression levels of CSPGs dramatically increased under 3D conditions. The relative *phosphacan* expression level on day 1 in the 3D condition increased by 17-fold compared to that on day 0 (adjusted p < 0.0001, ANOVA with Tukey's multiple comparison tests; Figure 2G). Additionally, the relative *brevican* and *tenascin-R* expression levels were high on day 1 under 3D conditions but barely detectable on day 0 or day 1 under 2D conditions (Figure 2 H, I).

Discussion

Oligodendrocyte differentiation markers, such as CNP and MBP, have been previously used to characterize immature and mature oligodendrocytes during OLP6 differentiation[6]. In this study, we found that mature oligodendrocyte markers were more rapidly expressed when OLP6 cells were allowed to differentiate on decellularized tissues rather than on commonly used coated surfaces. The production of CSPGs, such as tenascin-R, by oligodendrocytes has been implicated in neural cell recognition[13]. In addition, CSPGs, such as versican, are produced by oligodendrocyte lineage cells in response to an injury[14]. In this study, we report that the ECM expression profile of different CSPGs was significantly increased when OLP6 was differentiated on decellularized tissues. Although decellularized brain tissue has been previously used as a scaffold for the long-term growth of undifferentiated neural stem cells[11], to the best of our knowledge, the present study is the first to report oligodendrocyte cell line differentiation on decellularized brain tissues.

This preliminary study focused on the onset of OPC differentiation into mature oligodendrocytes. However, further studies in which OLP6 can be differentiated for a longer period are necessary to fully understand the benefit of growing them on decellularized tissue. Nonetheless, this study highlights a new model of 3D *in vitro* oligodendrocyte culture that contains ECM with all of its chemical and mechanical complexities. Our study provides important insights into the development of models to investigate the OPC/ECM interaction.

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Author contributions

KK, HN, RA, YY, and TT designed the study and wrote the manuscript, and AK and EAH supervised the work and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest. All experiments were conducted in compliance with the ARRIVE guidelines.

References

1) Nishiyama A, Suzuki R, Zhu X: NG2 cells (polydendrocytes) in brain physiology and repair. Front Neurosci, 2014; 8: 133.
2) Sakry D, Neitz A, Singh J, *et al*: Oligodendrocyte Precursor Cells Modulate the Neuronal Network by Activity-Dependent Ectodomain Cleavage of Glial NG2. PLoS Biol, 2014; 12: e1001993.
3) Buntinx M, Vanderlocht J, Hellimgs N, *et al*: Characterization of three human oligodendroglial cell lines as a model to study oligodendrocyte injury: Morphology and oligodendrocyte-specific gene expression. J Neurocytol, 2003; 32: 25-38.
4) Louis JC, Magal E, Muir D, Manthorpe M, Varon S: CG-4, A new bipotential glial cell line from rat brain, is capable of differentiating in vitro into either mature oligodendrocytes or type-2 astrocytes. J Neurosci Res, 1992; 31: 193-204.
5) Verity AN, Bredesen D, Vonderscher C, Handley VW, Campagnoni AT: Expression of Myelin Protein Genes and Other Myelin Components in an Oligodendrocytic Cell Line Conditionally Immortalized with a Temperature-Sensitive Retrovirus. J Neurochem, 1993; 60: 577-587.
6) Matsushita T, Amagai Y, Soga T, Terai K, Obinata M, Hashimoto S: A novel oligodendrocyte cell line OLP6 shows the successive stages of oligodendrocyte development: late progenitor, immature and mature stages. Neuroscience, 2005; 136: 115-121.
7) Karus M, Ulc A, Ehrlich M, *et al*: Regulation of oligodendrocyte precursor maintenance by chondroitin sulphate glycosaminoglycans. Glia, 2016; 64: 270-286.
8) Siebert JR, Osterhout DJ: The inhibitory effects of chondroitin sulfate proteoglycans on oligodendrocytes. J Neurochem, 2011; 119: 176-188.

9) Hu J, Deng L, Wang X, Xu XM: Effects of extracellular matrix molecules on the growth properties of oligodendrocyte progenitor cells in vitro. J Neurosci Res, 2009; 87: 2854–2862.
10) Segel M, Neumann B, Hill MFE, *et al*: Niche stiffness underlies the ageing of central nervous system progenitor cells. Nature, 2019; 573: 130–134.
11) De Waele J, Reekmans K, Daans J, Goossens H, Berneman Z, Ponsaerts P: 3D culture of murine neural stem cells on decellularized mouse brain sections. Biomaterials, 2015; 41: 122–131.
12) Hoshiba T, Chen G, Endo C, *et al*: Decellularized extracellular matrix as an in vitro model to study the comprehensive roles of the ECM in stem cell differentiation. Stem Cells Int, 2016; 2016: 6397820.
13) Probstmeier R, Stichel CC, Müller HW, Asou H, Pesheva P: Chondroitin sulfates expressed on oligodendrocyte-derived Tenascin-R are involved in neural cell recognition. Functional implications during CNS development and regeneration. J Neurosci Res, 2000; 60: 21–36.
14) Asher RA, Morgenstern DA, Shearer MC, Adcock KH, Pesheva P, Fawcett JW: Versican is upregulated in CNS injury and is a product of oligodendrocyte lineage cells. J Neurosci, 2002; 22: 2225–2236.

Original Articles

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Predictors of Major Adverse Cardiovascular and Cerebrovascular Events After Acute Coronary Syndromes: A Retrospective Observational Study Using YoMDB Database

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Objectives: Despite the rapid aging of the population in Japan, clinical predictors for major adverse cerebrovascular and cardiovascular events (MACCE) in patients with new onset of acute coronary syndromes (ACS) have not been well studied. This study therefore aimed to identify the predictors of MACCE in the first onset of ACS patients requiring care.

Materials and Methods: Using the Yokohama Original Medical Database, we identified 3,373 patients who experienced a first onset of ACS and had certified care information from April 2014 to March 2016. The incidence proportion of MACCE from June 2014 to March 2018 was retrospectively investigated. Each patient's independence of daily living (IDL) was classified as one of three categories (reference, mild and severe).

Results: Predictors of MACCE were identified using multivariate logistic regression analysis. Impaired IDL was associated with increased MACCE, with adjusted odds ratios for reference, mild and severe of 1.00, 1.35 (95% confidence intervals 1.14–1.60) and 2.12 (95% confidence intervals 1.61–2.80; P for trend < 0.001), respectively.

Conclusions: This study revealed that male sex, chronic kidney disease, atrial fibrillation, high-intensity statin use, low-intensity statin use, and lower IDL (representing less independence) were the predictors of MACCE requiring care for a first onset of ACS. Further research will be required to understand the results of interventions for the identified predictors of MACCE.

Key words: stroke, myocardial infarction, care, nursing

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Introduction

The role of long-term care insurance has become more important in Japan with the emergence of its super-aging society. The number of persons certified as requiring care under the long-term care insurance system has increased approximately 2.5 times since the start of the long-term care insurance system in 2000, from 2.56 million persons to approximately 6.41 million persons in 2018, and long-term care benefit expenditure has increased approximately 2.9 times, from 3.2 trillion yen ($23.7 billion) to 9.2 trillion yen ($68.1 billion), showing an especially rapid increase in the most recent data[1]. The average life expectancy of Japanese people is among the highest in the world. However, healthy life expectancy is considerably shorter, with a gap of approximately 9 years for men and approximately 12 years for women, meaning that many elderly people require support and care for some 10 years in late life. Cerebral and cardiovascular disease account for 16.6% and 4.6%, respectively, of the causes leading to this need for care, together representing the highest proportion, 21.2%, from any reported cause[2]. Therefore, the prevention of cerebral and cardiovascular disease is important for the suppression of expenditures on national healthcare and long-term care benefits.

National healthcare expenditure in Japan continues its increasing trend, and total national healthcare expenditure in 2018 was 43 trillion yen ($319 billion)[2]. When medical expenses are examined by injury/disease category resulting from primary injury/disease, cerebral and cardiovascular disease is the most expensive category, at 6.1 trillion yen ($44.9 billion; composition ratio: 19.3%), and among both men and women represents the greatest impact on medical expenses.

Among cardiovascular diseases, ischemic heart disease in the form of acute coronary syndromes (ACS) is often the cause of heart failure. Several studies conducted in Japan in patients with acute heart failure have reported that ischemic heart disease accounts for more than 30% of the major causative diseases leading to acute heart failure[3-7]. In another report of 7,733 patients aged 65 years or older who were hospitalized for a first onset of myocardial infarction without a history of heart failure, approximately 75% of patients developed heart failure within 5 years, and approximately 40% of them died[8]. These reports suggest that prevention of ACS may also contribute to preventing the development of heart failure.

In a recent registry study of ACS in Japan, 27%-40% of patients with ACS were reported to have cerebral or cardiovascular events within 3 years[9]. Independent predictors for 3-year major adverse cardiac events have been reported as higher age, dyslipidemia, chronic kidney disease, stroke, peripheral artery disease, previous myocardial infarction, and Killip class ≥ 2[10]. In addition, a prospective multicenter study investigating the prevalence and clinical outcomes of polyvascular disease including stroke in patients with ACS showed that ACS patients with polyvascular disease had poorer clinical outcomes, including recurrent myocardial ischemia, heart failure, stroke, and death, than did those without polyvascular disease[11]. Given these reports, suppression of recurrence of ACS or stroke means improving patient outcomes, but additionally has broad and important socio-economic implications. This concept is also consistent with addressing "secondary prevention" as outlined in the Cerebrovascular and Cardiovascular Disease Control Act, enacted in Japan in December 2018 as the first ever legislative countermeasure against stroke and cardiovascular disease in Japan, and is an important consideration for effective evidence-based policy making[12].

However, to our knowledge there has been no report on the associations between the recurrence of cerebral and cardiovascular disease and the degree of independence in daily living (IDL). Yokohama, one of the largest cities in Japan, has its own medical database, Yokohama Original Medical Database (YoMDB), based on long-term care insurance. Therefore, the present study was conducted using this database to clarify the clinical setting of major adverse cerebral and cardiovascular events (MACCE) and the predictors for MACCE in patients undergoing care for the first onset of ACS.

Materials and Methods

Database

Medical claims and long-term care data since April 2014 from YoMDB were used for this study[13]. YoMDB is a large medical invoice database that includes residents of Yokohama City who have one

of the following three insurance types: National Health Insurance, Medical Care System for Older Senior Treatment, and Public Assistance. Data for a single year include more than 30 million records, covering 86.4% of the entire population aged 65 years or older and more than 99% of the population aged 75 years or older in Yokohama City, where nearly 3.7 million people live. The total data for 2015 included 1,247,408 people and 14,944,496 medical invoices. Based on YoMDB's use policy, values less than 10 and those that were less than 10 after subtraction were omitted to avoid potential identification of individuals. This study used an opt-out system at the official website of Yokohama City, instead of obtaining informed consent from patients.

Subjects

The subjects included patients who received certification of need for support or long-term care at the end of each fiscal year from June 2014 to March 2018 and who had new onset of ACS during the 2 years from April 2014 to March 2016. Outcomes were MACCE between June 2014 and March 2018. MACCE was defined as all-cause death, ACS, or stroke with hospitalization receipt data for the primary disease name within 2 years after the onset of ACS. Patients with MACCE within 30 days after the first onset of ACS were excluded, given that there may be patients who have been hospitalized since the previous month. A first onset of ACS was defined as occurring in patients who had no ACS prior to 2014 and had ACS initiated between April 2014 and March 2016. For the purposes of patient background characteristics, the baseline was defined as the time of the first onset of ACS.

The study flow chart and baseline characteristics are shown in Figure 1 and Table 1, respectively. From a total of 32,267 patients in the YoMDB database who had a record of ACS in the 2 years from April 2014 to March 2016, after excluding 17,208 cases who had ACS recorded before April 1, 2014, we identified 15,059 cases. We then excluded 9,808 cases who did not receive care from March 2014 to March 2018; 5,251 cases remained. From these were excluded 273 subsequent cases that occurred within one month after the first onset of ACS and 1,605 patients for whom care certification information was not obtained throughout the observation period. Finally, 3,373 cases were extracted as the analysis set.

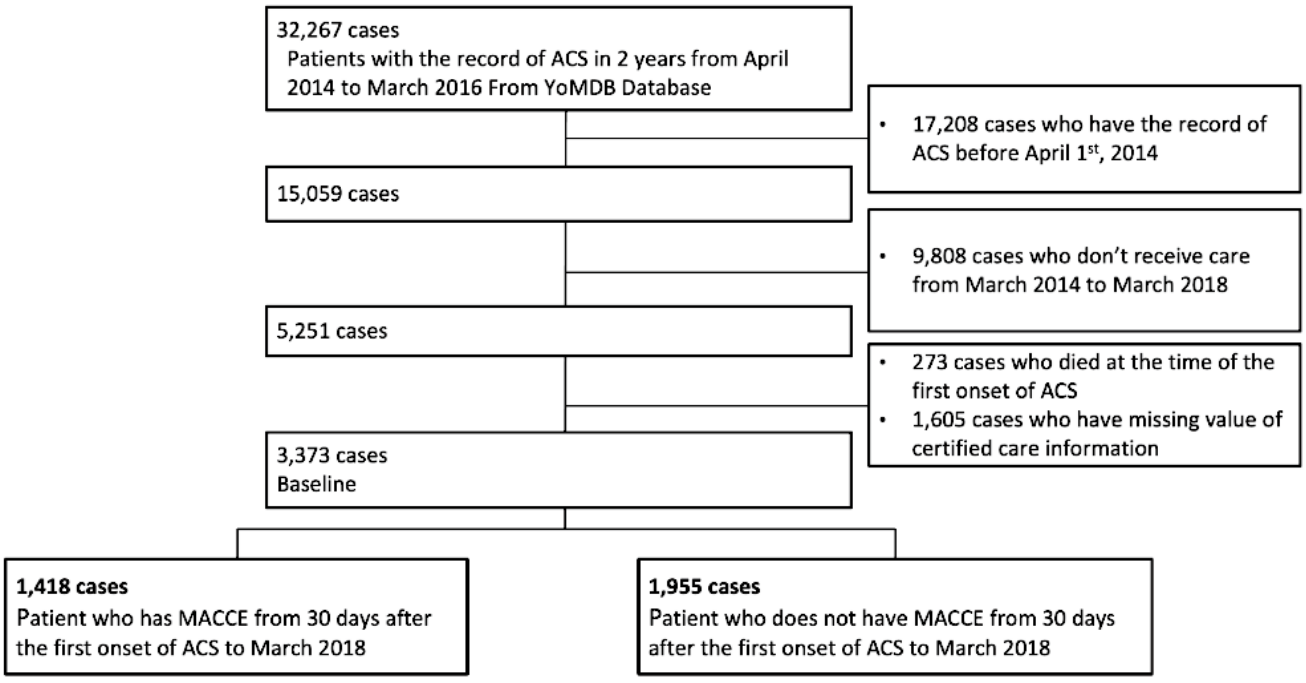

Figure 1 Study flow chart

ACS indicates acute coronary syndromes; YoMDB, Yokohama Original Medical Database; and MACCE, major adverse cerebrovascular and cardiovascular events. A total of 1,605 cases were excluded due to lack of certified care information, i.e., IDL rank.

Table 1 Baseline characteristics of 3373 subjects

Baseline characteristics (At first onset of ACS)	n	%
Age, mean (±SD) [years]	82.8 (± 7.4)	
≤ 64 years	56	1.7%
65–74 years	344	10.2%
75–84 years	1,510	44.8%
≥ 85 years	1,463	43.4%
Male sex	1,459	43.3%
Comorbidity (n, %)		
Stroke		
Stroke all	1,010	29.9%
Ischemic stroke	977	29.0%
Hemorrhagic stroke	55	1.6%
Peripheral artery disease (PAD)	109	3.2%
Hypertension	2,924	86.7%
Diabetes	1,040	30.8%
Dyslipidemia	1,603	47.5%
Carotid artery stenosis	290	8.6%
Chronic kidney disease (CKD)	421	12.5%
Atrial fibrillation (AF)	886	26.3%
Aortic valve stenosis	114	3.4%
Dementia	861	25.5%
Surgery (n, %)		
Coronary revascularization		
Total	418	12.4%
PCI (Percutaneous coronary intervention)	405	12.0%
CABG (Coronary artery bypass grafting)	13	0.4%
Transportation by ambulance (n, %)	1,101	32.6%
Medication (n, %)		
ARB (angiotensin II receptor blocker)	1,015	30.1%
ACEi (angiotensin converting enzyme inhibitor)	228	6.8%
Beta-blocker	496	14.7%
Low intensity statin	465	13.8%
High intensity statin	764	22.7%
Dementia drugs	407	12.1%
Antiplatelet/antithrombotic	2,301	68.2%
Single	1,389	41.2%
Double	826	24.5%
Triple	86	2.5%
Independence of daily living Category (Rank) (n, %)		
Reference (Independent, I, IIa)	2,080	61.7%
Mild (IIb, IIIa, IIIb)	1,015	30.1%
Severe (IV, M)	266	7.9%
Unknown	12	0.3%

Data extraction: Classification based on the IDL

The degree of IDL was based on the attending physician's opinion on "Degree of IDL for the elderly with dementia" recorded in the long-term care insurance certification information and was classified into one of three groups (Supplemental Table 1). Patients who were able to independently take medications were categorized as the Reference group, those needing assistance in taking medications as the Mild group, and the severely disabled as the Severe group. This status of independence was used as an explanatory variable in a multivariate logistic regression analysis.

Data extraction: Medical history, comorbidities, procedure, and IDL

Past medical history and comorbidities were extracted when there was a claim code indicating medical history and comorbidities prior to the first claim of ACS. Surgical procedure data were extracted when it was claimed in the same month as the first onset of ACS. Medications were extracted if they were prescribed in the month when the index disease started. The degree of IDL was extracted at the time point closest in end of March and September to the time of first onset of ACS.

Data extraction: Medication

Medication status was extracted when there was any prescription filled at discharge or pharmacy receipt on record. Details of definition and classification of each medication are shown in Supplemental Table 2.

Data extraction: ICD-10 code

The ICD-10 code for each disease name and procedure was extracted with details shown in Supplemental Table 3.

Statistical analysis

Predictors, odds ratios, and 95% confidence intervals of MACCE were analyzed using logistic regression analysis according to baseline characteristics. All independent variables, selected in accordance with the related research to date, were simultaneously introduced, and the incidence proportion of MACCE was used as a dependent variable. Missing values were handled by complete case analysis. P values of <0.05 were considered statistically significant. EZR statistical software (version 4.0.3), which extends the functionality of R and R Commander software, was used for all statistical analyses[14].

Ethical considerations

This study was conducted with the approval of the Juntendo University Institutional Review Board (Approval No. M20-0256-M01).

Results

Incidence proportion of MACCE

The incidence proportion of MACCE and baseline characteristics according to presence or absence of MACCE after follow-up are shown in Table 2. The incidence proportion of MACCE was 42.0% in patients with the first onset of ACS. Patients were classified into the 1,418 patients who had MACCE after 30 days from the first onset of ACS until March 2018, and the 1,955 patients who did not have MACCE during the above period. The incidence proportion of MACCE according to IDL rank are shown in Figure 2. The incidence proportion of MACCE in reference, mild and severe were 37.7%, 46.5% and 57.9%, respectively (P for trend < 0.001 by Cochran-Armitage test).

Multivariate analysis

The multivariate logistic regression analysis showed that male sex, concurrent chronic kidney disease, concurrent atrial fibrillation, taking high-intensity statins, taking low-intensity statins, and severe IDL (less independence) are independent predictors of MACCE (Table 3). Positive associations were observed between male sex, concurrent chronic kidney disease, concurrent atrial fibrillation, and MACCE. A positive association was also observed between the category of IDL and MACCE. Contrast negative associations were observed between taking high-intensity statins, taking low-intensity statins, and MACCE. Adjusted odds ratios and 95% confidence intervals (CI) for reference, mild and severe IDL were 1.00, 1.35 (95% CI 1.14-1.60) and 2.12 (95% CI 1.61-2.80; P for trend < 0.001), respectively (Figure 3).

Discussion

In the present study, risk factors for MACCE were determined using highly complete real-world

Table 2 Incidence proportion of MACCE and baseline characteristics according to presence or absence of MACCE during follow-up

	MACCE			
	Presence	%	Absence	%
All cases (n=3,373) (n, %)	1,418	42.0%	1,955	58.0%
Age (mean ± SD) [years]	83.6 ± 7.8		82.3 ± 7.1	
Age (n, %)				
≤ 64 years	23	1.6%	33	1.7%
65-74 years	135	9.5%	209	10.7%
75-84 years	580	40.9%	930	47.6%
≥ 85 years	680	48.0%	783	40.1%
Male (n, %)	718	50.6%	741	37.9%
Comorbidity (n, %)				
Stroke				
Stroke all	493	34.8%	517	26.4%
Ischemic stroke	475	33.5%	502	25.7%
Hemorrhagic stroke	30	2.1%	25	1.3%
Peripheral artery disease (PAD)	46	3.2%	63	3.2%
Hypertension	1,223	86.2%	1,701	87.0%
Diabetes	437	30.8%	603	30.8%
Dyslipidemia	618	43.6%	985	50.4%
Carotid artery stenosis	126	8.9%	164	8.4%
Chronic kidney disease (CKD)	229	16.1%	192	9.8%
Atrial fibrillation (AF)	432	30.5%	454	23.2%
Aortic valve stenosis	52	3.7%	62	3.2%
Dementia*	396	27.9%	465	23.8%
Surgery (n, %)				
Coronary revascularization				
Total	152	10.7%	266	13.6%
PCI (Percutaneous coronary intervention)	147	10.4%	258	13.2%
Transportation by ambulance (n, %)	486	34.3%	615	31.5%
Medication (n, %)				
ARB (Angiotensin II receptor blocker)	410	28.9%	605	30.9%
ACEi (Angiotensin converting enzyme inhibitor)	92	6.5%	136	7.0%
Beta-blocker	186	13.1%	310	15.9%
Low intensity statin	142	10.0%	323	16.5%
High intensity statin	284	20.0%	480	24.6%
Dementia drugs	179	12.6%	228	11.7%
Antiplatelet/antithrombotic	990	69.8%	1,311	67.1%
Single	606	42.7%	783	40.1%
Double	352	24.8%	474	24.2%
Triple	32	2.3%	54	2.8%
Independence of daily living Category (Rank) (n, %)				
Reference (Independent, I, IIa)	785	55.4%	1,295	66.2%
Mild (IIb, IIIa, IIIb)	472	33.3%	543	27.8%
Severe (IV, M)	154	10.9%	112	5.7%

*: Dementia, as comorbidity, was derived from claim database, which was diagnosed by clinical physician.

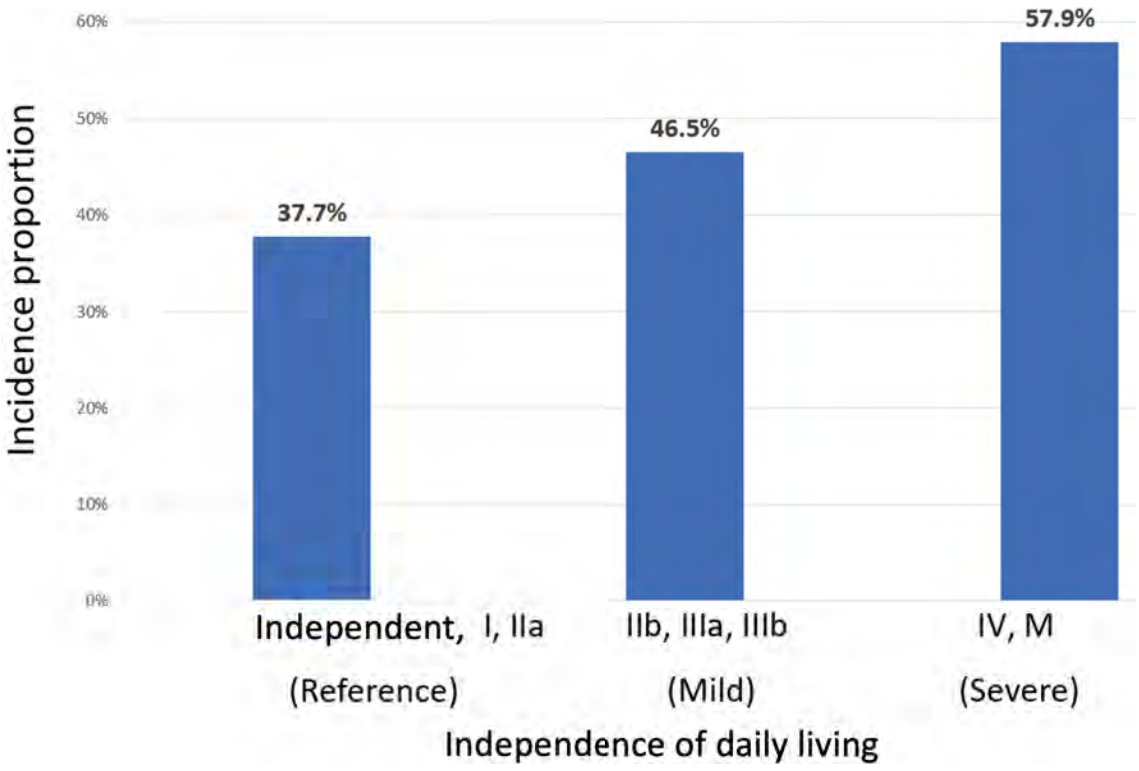

Figure 2 Rank of IDL and incidence proportion of MACCE
IDL rank and incidence proportion of MACCE. This analysis excludes 12 patients whose degree of independence of daily life was unknown. Classification of IDL rank is shown in Supplemental Table 1. IDL, independence of daily living; MACCE, major adverse cerebrovascular and cardiovascular events.

data from YoMDB database. A multivariate logistic regression analysis showed that male sex, concurrent chronic kidney disease, concurrent atrial fibrillation, high-intensity statin use, low-intensity statin use, and a high category of IDL (signifying less independence) were predictors of MACCE. Also, degree of IDL was associated with the incidence proportion of MACCE.

Predictors of MACCE

The predictors of MACCE revealed in this study are in accord with previous research. Many studies have shown that the incidence proportions of MACCE and their sequelae are higher in males than in females. Similarly, CKD is a known high-risk condition of arteriosclerotic disease that has been associated with an increased risk of cardiovascular events[15, 16]. Atrial fibrillation is associated with increased cardiovascular risk[17], and many previous studies have reported the effect of statins on MACCE[18]. We may need to consider the background and severity of patients when interpreting the odds ratios in the high-intensity statin group and the low-intensity statin group in this study, as the odds ratios seem to be the inverse of what would be anticipated, i.e., this may be because severe patients in whom the risk of MACCE is difficult to reduce are prone to use high-intensity statin because of its complexity. These previously known risk factors were confirmed as predictors of MACCE in this population with newly diagnosed ACS requiring interventional care.

Relationship between long-term care and MACCE

According to National Health Care Coverage data, in fiscal year 2018, the total percentage of causative diseases requiring support/long-term care was 18.5% for cerebrovascular disease and 4.5% for cardiovascular disease, and the total number for cerebral and cardiovascular diseases was 23.0%. The proportion increases as the level of need for long-term care rises. Cerebral and cardiovascular disease accounted for the highest proportion, 35.9%, of the level 5 cases requiring long-term care, which is the highest care requirement[19]. Furthermore, it has been reported that the level of long-term care required often progresses irreversibly in a stepwise manner from support to long-

Table 3 Odds ratios and 95% confidence intervals (CIs) of MACCE according to baseline characteristics by multivariate logistic regression analysis

Independent variables	Univariate				Multivariate			
	Odds ratio	95% CI lower limit	95% CI upper limit	p-value	Odds ratio	95% CI lower limit	95% CI upper limit	p-value
Gender								
Female	Referent				Referent			
Male	1.68	1.46	1.93	<0.001	1.66	1.43	1.92	<0.001
Age								
≤ 64 years	Referent				Referent			
65 -74 years	0.92	0.52	1.63	0.76	1.14	0.63	2.06	0.67
75 -84 years	0.89	0.52	1.54	0.68	1.22	0.69	2.15	0.48
≥ 85 years	1.25	0.72	2.14	0.42	1.69	0.95	2.98	0.072
Comorbidity*								
Hypertension	0.94	0.77	1.15	0.52	0.96	0.77	1.19	0.68
Diabetes	1.00	0.86	1.15	0.94	1.04	0.88	1.22	0.64
Dyslipidemia	0.76	0.66	0.87	<0.001	0.88	0.75	1.03	0.10
Peripheral artery disease (PAD)	1.03	0.70	1.51	0.89	1.11	0.74	1.66	0.62
History of stroke all	1.49	1.29	1.73	<0.001	1.84	0.89	3.78	0.098
History of ischemic stroke	1.47	1.26	1.70	<0.001	0.79	0.38	1.63	0.51
Carotid artery stenosis	1.07	0.84	1.37	0.56	1.00	0.77	1.30	0.98
Chronic kidney disease (CKD)	1.76	1.43	2.16	<0.001	1.76	1.41	2.18	<0.001
Atrial fibrillation (AF)	1.44	1.24	1.68	<0.001	1.31	1.11	1.55	0.001
Aortic valve stenosis	1.17	0.80	1.70	0.42	1.30	0.88	1.93	0.18
Dementia	1.24	1.06	1.45	0.006	1.04	0.84	1.29	0.71
Transportation by ambulance	1.14	0.98	1.32	0.086	1.05	0.90	1.23	0.53
Medication*								
ARB (Angiotensin II receptor blocker)	0.91	0.78	1.06	0.21	0.98	0.84	1.16	0.83
ACEi (Angiotensin converting enzyme inhibitor)	0.94	0.71	1.23	0.64	0.99	0.74	1.32	0.93
Beta-blocker	0.80	0.66	0.98	0.028	0.86	0.70	1.06	0.15
Low-intensity statin	0.56	0.46	0.69	<0.001	0.59	0.47	0.75	<0.001
High-intensity statin	0.77	0.65	0.91	0.002	0.80	0.66	0.98	0.028
Dementia drugs	1.10	0.89	1.36	0.36	0.93	0.71	1.22	0.60
Antiplatelet/antithrombotic Single	1.11	0.97	1.28	0.12	1.08	0.91	1.30	0.37
Antiplatelet/antithrombotic double	1.03	0.88	1.21	0.68	1.18	0.95	1.47	0.13
Antiplatelet/antithrombotic Triple	1.17	0.80	1.70	0.42	1.30	0.88	1.93	0.18
IDL: Independence of daily living								
Category: **Reference** (Rank: Independent, I, IIa)	Referent				Referent			
Category: **Mild** (Rank: IIb, IIIa, IIIb)	1.43	1.23	1.67	<0.001	1.35	1.14	1.60	<0.001
Category: **Severe** (Rank: IV, M)	2.27	1.75	2.94	<0.001	2.12	1.61	2.80	<0.001

Objective variable: MACCE

*Referent of variables in comorbidity and medication are no comorbidity and no medication.

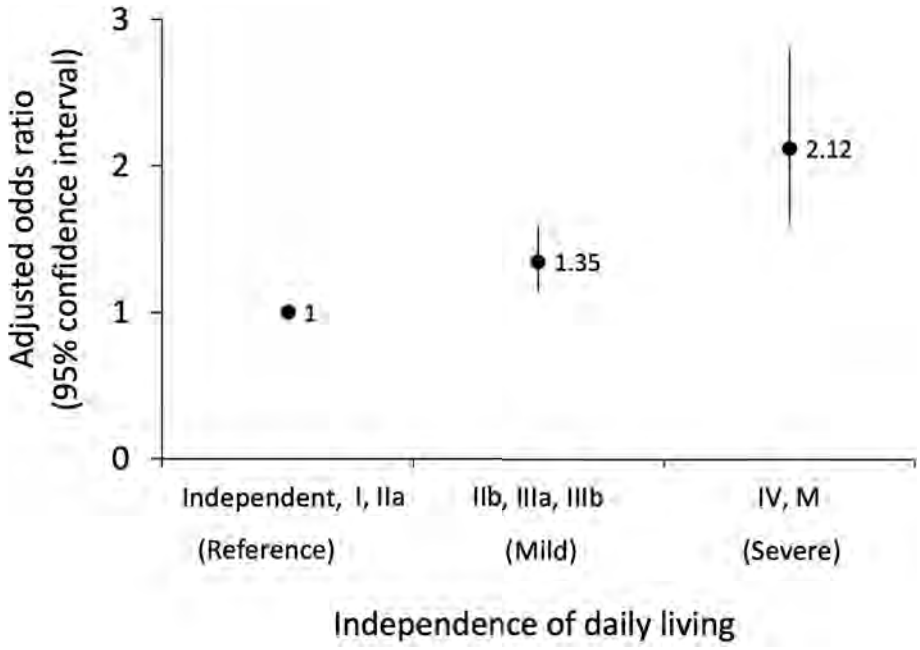

Figure 3 IDL category and adjusted odds ratios of MACCE
IDL category and adjusted odds ratios of MACCE with 95% confidence interval. This analysis excludes 12 patients whose degree of independence of daily life was unknown. Classification of IDL category is shown in Supplemental Table 1. IDL, independence of daily living; MACCE, major adverse cerebrovascular and cardiovascular events.

term care needs[20].

Given these reports, the secondary occurrence of cerebral and cardiovascular events is one of the factors influencing the progression of the level of care needed. Therefore, it may be important to prevent recurrence or subsequence of cerebral and cardiovascular events to prevent this progression.

Relationship between IDL and MACCE

Prior reports on patient frailty may be of use in interpreting the relationship between the degree of independence of daily living and cerebral and cardiovascular events revealed in this study. Frailty, recently identified as being characteristic of the physical and mental state of the elderly, is defined as a state intermediate between health and requiring care[21]. Frailty has been shown to be associated with impaired activities of daily living, hospitalization, and life expectancy, and the presence of frailty has also been reported as a risk factor for certification of long-term care needs[22]. Patients with cardiovascular disease have a 2.7–4.1-fold higher prevalence of frailty and a 1.5-fold higher longitudinal incidence; in addition, patients with coronary artery disease or heart failure who also have frailty have a 1.6–4-fold increased risk of death[23].

Thus, the relationship between frailty and cerebral and cardiovascular diseases has already been clarified in several studies. In other words, the condition in which daily life is more independent may lead to the suppression of subsequent cerebral and cardiovascular events, and interventions for the controllable predictors shown in this study may aid in the suppression of progression to needing a greater level of care. Furthermore, such interventions for suppression of MACCE may also extend healthy life expectancy.

Limitations of this study

This study has several limitations. First, there is a possibility of incurring some selection bias by limiting cases to those for which long-term care certification information is available. Second, detailed information such as smoking habits, body mass index, and various laboratory test values are unavailable in the YoMDB database, and the severity and control status of ACS and each comorbidity are not taken into consideration. Third, each comorbidity and medication selected as an explanatory variable may have been over-evaluated because of the criteria to pick up, i.e., the existence of any prescrip-

tion filled, and no validation for that. Forth, this study has no detailed information on ADL such as Barthel Index, which is crucial to fully understand the association between MACCE and frailty. Fifth, the association between MACCE and IDL as history of included stroke patients may have some bias, even though this was adjusted as an explanatory variable in the logistic regression analysis. Finally, further research will be required to understand the results of interventions for the identified predictors of MACCE, as investigating the clinical impact of such interventions is beyond the scope of this study.

Conclusion

In patients with a first onset of ACS, male gender, chronic kidney disease, atrial fibrillation, high-intensity statin use, low-intensity statin use, and lower IDL were predictors of MACCE. The higher level of care a patient needed, the more likely MACCE was to occur. Therefore, given the current and projected future care needs, as well as previous studies, interventions for controllable factors may be effective in reducing the incidence of MACCE in patients with the first onset of ACS.

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Author contributions

YH was a major contributor in writing the manuscript. SN (Sachiko Nakagami), TC, and SD provided YoMDB database and performed statistical analysis. HI, YN, SN (Shuko Nojiri), and YS provided advice and guidance. KY supervised this study and provided advice and guidance. All authors read and approved the final manuscript.

Conflicts of interest statement

YH is an employee of Amgen K.K.

References

1) Ministry of Health, Labour and Welfare: Outline of Estimates of National Medical Care Expenditure 2018. https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa18/index.html (Accessed July 2, 2022) (in Japanese)
2) Ministry of Health, Labour and Welfare: Comprehensive survey of living conditions 2019. https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa19/index.html (Accessed July 2, 2022) (in Japanese)
3) Adams KF Jr, Fonarow GC, Emerman CL, *et al*: Characteristics and outcomes of patients hospitalized for heart failure in the Unite-d States: Rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J, 2005; 149: 209-216.
4) Kawashiro N, Kasanuki H, Ogawa H, Matsuda N, Hagiwara N: Clinical characteristics and outcome of hospitalized patients with congestive heart failure: results of the HIJC-HF registry. Circ J, 2008; 72: 2015-2020.
5) Nieminen MS, Brutsaert D, Dickstein K, *et al*: EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Euro Heart J, 2006; 27: 2725-2736.
6) Sato N, Kajimoto K, Keida T, *et al*: Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). Circ J, 2013; 77: 944-951.
7) Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, Goto G, Takeshita A: Clinical characteristics and outcome of hospitalized patients with heart failure in Japan. Circ J, 2006; 70: 1617-1623.
8) Ezekowitz JA, Kaul P, Bakal JA, Armstrong PW, Welsh RC, McAlister FA: Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol, 2009; 53: 13-20.
9) Ishihara M, Nakao K, Ozaki Y, *et al*: Long-Term Outcomes of Non-ST-Elevation Myocardial Infarction Without Creatine Kinase Elevation - The J-MINUET Study. Circ J, 2017; 81: 958-965.
10) Kimura T, Akahori H, Asakura M, *et al*: Impact of Age on Gender Difference in Long-term Outcome of Patients With Acute Myocardial Infarction (from J-MINUET). Am J Cardiol, 2021; 142: 5-13.
11) Al Thani H, El-Menyar A, Alhabib KF, *et al*: Polyvascular disease in patients presenting with acute coronary syndrome: its predictors and outcomes. Scientific World Journal, 2012; 2012: 284851.
12) Kuwabara M, Mori M, Komoto S: Japanese National Plan for Promotion of Measures Against Cerebrovascular and Cardiovascular Disease. Circulation, 2021; 143: 1929-1931.
13) Suzuki Y, Dohmae S, Ohyama K, Nishio H, Fujii H, Shuri J: Demand for home medical care will continue to increase in the next decades: An analysis from the Yokohama Original Medical Database (YoMDB). Geriatr Gerontol Int, 2018; 18: 1578-1579.
14) Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant, 2013; 48: 452-458.
15) GBD Chronic Kidney Disease Collaboration: Global, regional, and national burden of chronic kidney disease,

1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet, 2020; 395: 709–733.
16) Weiner DE, Tighiouart H, Amin GM, *et al*: Chronic Kidney Disease as a Risk Factor for Cardiovascular. J Am Soc Nephrol, 2004; 15: 1307–1315.
17) Odutayo A, Wong XC, Hsiao JA, Hopewell S, Altman DG, Emdin CA: Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ, 2016; 354: i4482.
18) Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP: Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels: A Meta-analysis. JAMA Cardiol, 2018; 3: 823–828.
19) Ministry of Health, Labour and Welfare: Overview of National Health Care Coverage in Fiscal 2018. https://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/18/index.html (Accessed July 2, 2022) (in Japanese)
20) Osada H, Harada Y, Azemoto C, Wakui Y: Change in Care-Needs Level Overtime: Change in the Distribution of Care-Needs Level in the Same Population over 9 Years. Kousei no Shihyou (Journal of health and welfare statistics), 2011; 58: 37–43. (in Japanese)
21) Kuzuya M: Impact of sarcopenia and frailty on elderly health. Nihon Ronen Igakkai Zasshi, 2009; 46: 279–285. (in Japanese)
22) Shimada H, Makizako H, Doi T, Tsutsumimoto K, Suzuki T: Incidence of Disability in Frail Older Persons With or Without Slow Walking Speed. J Am Med Dir Assoc, 2015; 16: 690–696.
23) Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP, Bergman H: Role of frailty in patients with cardiovascular disease. Am J Cardiol, 2009; 103: 1616–1621.
24) Hirayama A, Honarpour N, Yoshida M, *et al*: Effects of evolocumab (AMG145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk-primary results from the phase 2 YUKAWA study. Circ J, 2014; 78: 1073–1082.
25) Nakamura M, Kimura K, Kimura T, *et al*: JCS 2020 Guideline Focused Update on Antithrombotic Therapy in Patients With Coronary Artery Disease. Circ J, 2020; 84: 831–865.

Supplemental Table 1 Classification based on the independence of daily living (IDL)*

Code	IDL rank	Category
1	Independent	1: Reference
2	I	
3	IIa	
4	IIb	2: Mild
5	IIIa	
6	IIIb	
7	IV	3: Severe
8	M	

*: "Degree of IDL for the elderly with dementia" was referred for this study because it was more suitable for the population of this study than "Degree of IDL for the disabled elderly".

Supplemental Table 2 Definition and classification of each medication

Classification	Definition
High-intensity statin	Any of daily atorvastatin ≥ 10 mg, pitavastatin ≥ 2 mg, rosuvastatin ≥ 5 mg, simvastatin ≥ 20 mg, fluvastatin ≥ 80 mg, pravastatin ≥ 40 mg, or any statin (even at low intensity) plus ezetimibe[24].
Antithrombotic drugs: Single therapy	An oral anticoagulant (OAC) alone (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) or single antiplatelet therapy (SAPT) (aspirin/P2Y12 receptor blocker (ticlopidine, clopidogrel, prasugrel, or ticagrelor))[25].
Antithrombotic drugs: Double therapy	OAC plus clopidogrel/prasugrel or dual antiplatelet therapy (DAPT)[25].
Antithrombotic drugs: Triple therapy	OAC plus DAPT. Two or more OACs were regarded in the same manner as one drug, and SAPTs other than clopidogrel/prasugrel were regarded as clopidogrel/prasugrel[25].

Supplemental Table 3 ICD-10 code of each disease name and procedure

Disease	ICD-10 code
Acute coronary syndrome	I 20.0, I 21.1-21.4, I 21.9, I 22.0, I 22.1, I 22.8-9, I 24.9
Heart failure	I 50.0-50.1, I 50.9, I 11.0, I 13.0, I 13.2
Pulmonary embolism	I 26.0, I 26.9
Acute aortic dissection or aortic aneurysm	I 71.0-71.9
Diabetes mellitus (type 1 and 2 diabetes mellitus)	E 10-11
Atrial fibrillation	I 480-482, I 489
Dementia	G 300-301, G 308-309, G 318, F 019, F 03
Alzheimer dementia	G 300-301, G 308-309
Dementia with Lewy Bodies	G 318
Cerebrovascular dementia	F019
Hypertension	I 10
Peripheral artery disease	I 739
Stroke	I 619, I 639, I 64
Chronic kidney disease	N 189
Dyslipidemia	E 785
Pneumonia	J 10-18
Malignant tumor	C 00-C 97
Cerebral hemorrhage	I 619
Cerebral infarction	I 638-639, I 64
PCI	K 546-550, K 550-2
CABG	K 552, K 552-2

Reviews

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Review of Performance Improvement of a Noninvasive Brain-computer Interface in Communication and Motor Control for Clinical Applications

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Brain–computer interfaces (BCI) enable direct communication between the brain and a computer or other external devices. They can extend a person's degree of freedom by either strengthening or substituting the human peripheral working capacity. Moreover, their potential clinical applications in medical fields include rehabilitation, affective computing, communication, and control. Over the last decade, noninvasive BCI systems such as electroencephalogram (EEG) have progressed from simple statistical models to deep learning models, with performance improvement over time and enhanced computational power. However, numerous challenges pertaining to the clinical use of BCI systems remain, e.g., the lack of sufficient data to learn more possible features for robust and reliable classification. However, compared with fields such as computer vision and speech recognition, the training samples in the medical BCI field are limited as they target patients who face difficulty generating EEG data compared with healthy control. Because deep learning models incorporate several parameters, they require considerably more data than other conventional methods. Thus, deep learning models have not been thoroughly leveraged in medical BCI. This study summarizes the state-of-the-art progress of the BCI system over the last decade, highlighting critical challenges and solutions.

Key words: brain–computer interface, medicine, deep learning, machine learning, data augmentation

Introduction

Brain–computer interface (BCI) can connect the brain and the external world by identifying brain activity and translating it into messages or commands, without depending on normal peripheral nerves and muscles[1)]. In particular, electroencephalogram (EEG) as noninvasive BCI has been developed for clinical purposes. For instance, EEG-based BCI has potential applications in the rehabilitation of patients suffering from stroke[2)], tactile system of communication and control options for patients with impairments of eye movements or vision[3)], and prognosis for patients with cognitive motor dissociation[4)]. However, challenges and limitations of BCI systems in clinical use still prevail.

Herein, we focus on BCI studies published between 2011 and 2021 to investigate the most recent trends in BCI research in the area of communication and control for clinical applications, such as the extraction of action intentions and translation into electrical commands and the monitoring of human physiology in patients with motor disabilities. Further, this study discusses the challenges and limitations

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of BCI systems along with solutions to these issues. This study also suggests future research for introducing BCI systems to medical fields.

Methods

In this mini-review, we investigate papers published in the past 10 years (January 2011–January 2021) that have been cited more than 100 times to refine search articles with high impact according to the Web of Science database. Papers with headings, abstracts, or keywords including the phrase "brain–computer interface" have been selected, and it has been ensured that the type of document is "article" rather than proceedings paper or review.

Performance Evaluation

Although many evaluation metrics have been used to quantify performance in the BCI field, the most common metric is classification accuracy[5, 6], which allows the measurement of the number of trials classified correctly as a percentage of all trials. Therefore, the accuracy obtained for each subject is used to evaluate existing BCI systems in this study. In a previous report, a BCI system with an accuracy of <70% was deemed unacceptable, whereas a BCI system with an accuracy of >75% was deemed successful[7]. Based on this report, the accuracy criteria were defined to compare existing BCIs (Table 1) in the present study.

BCI systems can be validated both offline and online. An offline approach validates a BCI system by using a dataset that has already been collected and shared by a few research groups. In most cases, the validation of a BCI system begins with identifying appropriate signal processing techniques offline. A subsequent online analysis is used to validate the performance of the BCI system for extracting and classifying trials from real data. Real-time embedded EEG-based brain–computer interface can be used for controlling electrical devices using EEG signals, which is an online approach.

Review of BCI Applications

This section introduces the selected papers, enabling a comprehensive understanding of the trend in the history and evolution of BCI systems to date in terms of the preprocessing and classifier models based on EEG signals.

EEG signals were developed[8] to extract thinking actions and translate them into electrical commands to develop an embedded BCI system that can be

Table 1 BCI performance summary

Reference	Year	Algorithms	Signal type	Accuracy (%)	Performance	Online/Offline
8)	2016	Hamming window, STFT, PCA, Linear regression	Translate thinking actions into electrical commands	74.6	Fair	Online
9)	2014	FFT, SLIC	Translate thinking actions into electrical commands	70.0	Fair	Offline
10)	2015	Theta spectra, threshold	Translate the physiological state into music selection	71.4	Fair	Online
11)	2017	Band-pass filter, average power, temporal correlation	Translate thinking actions into hand movements	70.0	Fair	Offline
12)	2016	DWT, SVM	Translate thinking actions into hand movements	82.1	Good	Offline
13)	2019	SCSSP, MI, LDA, SVM	Translate thinking actions into hand movements	81.9	Good	Offline
14)	2018	CNN	Translate thinking actions into hand movements	70.0	Fair	Online
15)	2019	CNN	Translate thinking actions into hand movements	80.5	Good	Offline
16)	2020	LSTM	Translate thinking actions into hand movements	97.6	Good	Offline

Abbreviation: STFT, short-time Fourier transform; PCA, primary component analysis; FFT, fast Fourier transform; SLIC, stimulus-locked inter-trace correlation; DWT, discrete wavelet transform; SVM, support vector machine; SCSSP, Separable Common Spatiospectral Pattern; MI, mutual information; LDA, linear discriminant analysis; CNN, convolutional neural network; LSTM, long short-term memory.

used to control electrical devices. The input EEG signals were filtered using an EEG filter block that extracts essential features and were converted into electric commands to activate the corresponding actions intended by the patient with severe motor disorders. The classification accuracy of translation into electrical commands was 74.6% based on linear regression via the online approach.

For improved biopotential acquisition and processing, an autonomous embedded BCI system was developed[9] based on an ARM9 processor that can port a real-time operating system for visual-evoked potentials. The results show that this application recovered visual evoked potentials using fast Fourier transform (FFT) by extracting frequency-domain features from BCI signals and stimulus-locked interlace correlation (SLIC); thus, a classification method based on EEG signals in the time domain was proposed. Additionally, the classification accuracy was found to be 70% upon examination of the steady-state visual-evoked potential phase-locking and time-locking in terms of the stimulus properties via the offline approach.

Further, a BCI-based smart multimedia controller was introduced[10], which can select music in different situations according to the user's physiological state. The multimedia platform in that study comprised an easily available commercial mobile tablet and a wireless multichannel EEG acquisition module designed for real-time EEG monitoring. A smart multimedia control program built into the multimedia platform was successfully developed to analyze the user's EEG and select music based on the user's physiological state. The experimental results show a classification accuracy of 71.4% via the online approach. The wireless multichannel EEG acquisition module can easily communicate with any type of commercial tablet via Bluetooth, thereby increasing acceptability among a large user demographic. Therefore, this BCI system is versatile and can be used on different evoked potential scenarios, such as medical brain-computer interfaces, while satisfying the strict real-time constraints that they impose.

However, BCI systems developed in previous studies were expensive and had limited portability; thus, the applications of BCI systems were limited. To address the lack of portability and high cost issues of BCI systems, a portable, low-cost BCI was developed and compared with a conventional BCI[11]. Specifically, five subjects were tested who were cued to alternate between hand opening/closing or were motionless while the BCI decoded their state of movement in real-time. The performance in each trial was defined as the temporal correlation between the cues and the decoded states. The results show that the EEG data acquired using the proposed and conventional BCIs were highly correlated (ρ = 0.79). The decoding performances, obtained using linear discriminant analysis, of the proposed and conventional BCIs were 70% and 68% in the offline approach, respectively, when averaged across trials and subjects; thus, the performances were not significantly different from each other.

Although previous studies used conventional and statistical classification models[12], introduced machine learning models such as support vector machines (SVM) for BCI systems. There is a background that the computer system had enough computational resources for fully embedded BCI systems. The classification result of a 2-class motor imagery paradigm was 82.1% using the SVM classifier and minimal processing time (0.11 s) in the offline approach on the embedded device in the experimental result, allowing the development of a portable, low-cost, and trustworthy system. Similarly[13], proposed a BCI system based on an SVM classifier. The proposed method includes statistical learning methods such as mutual information (MI), LDA, and SVM and applies the separable common spatiospectral pattern (SCSSP) method to extract features to design an accurate algorithm. The classification accuracy of a two-class motor imagery paradigm was 81.9% in the offline approach. The proposed BCI system achieves not only excellent recognition accuracy but also remarkable implementation efficiency in terms of portability, power, time, and cost.

Recently, deep learning techniques have been employed to improve the performance of BCI systems. Deep learning models can express more subtle and complex features in EEG signals than traditional machine learning techniques. Therefore, deep learning models are expected to provide more accurate predictions. A BCI system was[14] developed using the convolutional neural network (CNN) EEGNet, a compact version of the existing CNN,

for feature extraction and classification of motor imagery. As EEGNet is based on depthwise convolutional and separable convolution, the number of parameters in EEGNet is reduced. The EEG signals were processed as a series of multichannel images in a continuous-time domain showing the energy changes in the cerebral cortex during motor imagery of the subjects. The classification accuracy reached approximately 70.0%. To improve this system, a field-programmable gate array (FPGA) accelerator system[15] was proposed, which combines both flexibility and reconfigurability of different CNN structures. Applying the synchronous dataflow model to an embedded system and configuring the intellectual property cores of each layer separately, a 16-bit fixed-point CNN was finally used for EEG classification. The classification accuracy reached 80.5%, and the proposed design was approximately eight times faster and more efficient than the conventional BCI system in terms of execution time and power consumption. In another study, a BCI system with deep learning specialized in time series data called long short-term memory (LSTM) was proposed[16] to improve the quality of life for patients with motor disabilities. The proposed BCI system used multiple convolutional LSTM and fully-connected layers to decode EEG signals to maximize human intention recognition accuracy. The classification accuracy for a two-class motor imagery paradigm was 97.6% in the offline evaluation. Moreover, the proposed model reduces power consumption by 62.7% and improves the throughout power (W) by 168% compared with the previous models using central processing units, graphics processing units, field programmable gate arrays, application-specific integrated circuits, resistive random access memories, and photonic neural network accelerators.

Therefore, the BCI system has evolved from a simple statistical model to a deep learning model, and its performance has improved with time and the enhancement of computational power in computers.

Challenges and Limitations

Many BCI achievements in the SLIC application field have been reported. Furthermore, benchmark datasets can achieve state-of-the-art performance with high classification accuracy. However, most achievements have been validated using only the offline rather than the online approach. The performance in EEG trial classification obtained via the offline approach significantly decreases compared with that of the online approach[17]. For example, BCI was developed[18], enabling a controlled functional electrical stimulation (FES) based on EEG owing to stroke for re-establishing foot dorsiflexion. The study generated a prediction model based on approximate information discriminant analysis to classify EEG data into either "idling" or "dorsiflexion" stages; this information was subsequently used to control an FES device to elicit effective foot dorsiflexion. Although the average offline classification was 98.8%, the average online classification was 50%[19]. using two types of oddball paradigms, including the silk-stim paradigm (SSP) and linen-stim paradigm (LSP). The offline classification accuracies based on Bayesian linear discriminant analysis of the two paradigms for SSP and LSP were 64.5% and 75.5%, respectively, whereas the online classification accuracies were 50.0% and 53.0%, respectively. The steady-state visual-evoked potential-based BCI performance investigated under different perturbations[20]. The subjects focused on one of the four circles and provided feedback on the correctness of the classification under four conditions that were randomized across the subjects: *Control* (no perturbation), *Speaking* (counting loudly and repeatedly from 1 to 10), *Thinking* (mentally counting repeatedly from 1 to 10), and *Listening* (listening to verbal counting from 1 to 10). Although the offline mean classification accuracy using decision tree was 97.0%, the online mean classification accuracy was 83.0%.

Therefore, the accuracy of BCI systems decreases by approximately 20.0%–50.0% during the validation of the EEG signal processing chain based on the online approach. This could be attributed to the lack of sufficient data for rendering the classifier more robust and reliable. Compared with that in computer vision and speech recognition fields, the training samples in the medical BCI field are limited, as patients whose EEG data collections are limited compared with healthy controls are targeted. Additionally, the deep learning models require much more data than other conventional methods[21, 22] and cannot fully utilize the potential of the deep learning model in the medical BCI field.

Solution for the Problem

To overcome the prevalent data deficiency problems, novel approaches have been proposed to generate artificial brain signals and improve the performance of BCI systems. The first method was proposed by Fabien, which was implemented using mixing signal segmentation in the time domain[23]. This approach can significantly increase classification accuracy even for small training datasets. However, this approach poses the limitation of causing inadequate high-frequency noise at the boundary between two different segmentations. To overcome this problem, artificial EEG signal generation methods based on time-frequency representation (TFR) and analogy methods were proposed[24]. The aforementioned approach only considered the temporal features of EEG signals, not the frequency features. Therefore, an empirical mode decomposition method was proposed[25] to consider the features in the temporal and frequency domains. To further improve the classification accuracy, the differential entropy feature was used to generate more EEG signals, and this method could significantly improve the performance of deep learning models (LeNet and ResNet)[26].

Although all previous methods for generating artificial EEG signals were based on a combination of the features of raw EEG signals in different trials, various novel deep learning methods have recently been proposed to generate artificial EEG signals from the probability distribution and deep learning perspective rather than physically combining the effective features such as the signal segment, TFR, intrinsic mode function, or differential entropy. This data generation method is known as a generative adversarial network (GAN), and it can approximate the feature distribution of raw EEG signals during process training[27]. While GAN-based methods have been applied in computer vision for various purposes, such as generating images from text[28], generating videos with scene dynamics[29], and translating from image to image[30], this novel method has been implemented in the field of BCI to improve the BCI system performance.

For example, Roy et al.[31] leveraged the original version of GAN for BCI to classify trials based on the left- and right-hand motor imagery. The time-frequency characteristics of real and artificial EEG signals were compared using the short-term Fourier transform and Welch's power spectral density for evaluation. The results showed that GANs can capture important features of motor imagery EEG data, such as power variations, and that the power variation between the raw and artificially generated EEG signals was in the same frequency bin of Welch's power spectral density. Pascual et al.[32] used conditional Least Squares GAN (LSGAN) to alert caregivers and reduce the impact of seizures on patients' quality of life for epilepsy manifested by recurrent unprovoked seizures. LCGAN generated synthetic seizure-like EEG signals to train seizure detection and subsequently improved the detection performance by 1.2% overall relative to training only with real samples. Furthermore, Zhang et al. proposed a conditional deep convolutional GAN (cDCGAN) method for generating a large number of artificial EEG signals for data augmentation to improve CNN performance and overcome the problems associated with small training datasets. For the CNN model, the raw EEG signal was transformed into TRF to learn the time-frequency features from the TFR of the raw EEG signal using a two-dimensional kernel. Thus, cDCGAN is used to generate artificial TFR from the EEG signal and subsequently inverse the wavelet transform to generate waveform EEG signal. Therefore, data augmentation based on cDCGAN improved the classification accuracy of motor imagery tasks of the left- or right-hand movements from 82.8% to 85.8%[33]. Furthermore, the proposed methods were[34] based on two deep generative models (variational autoencoder (VAE) and GAN) and two augmentation strategies (Figure 1). The full usage strategy appended all generated data to the training dataset without judging the quality of the generated data, whereas partial usage selected only high-quality data and appended the data to the training dataset. These three methods are known as conditional Wasserstein GAN (cWGAN), selective VAE (sVAE), and selective WGAN (sWGAN). The effectiveness of these models was evaluated through a systematic experimental study on two public EEG datasets for emotion recognition, such as SEED and DEAP. First, realistic EEG training data were generated in two forms, such as power spectral density and differential entropy. Subsequently, the original

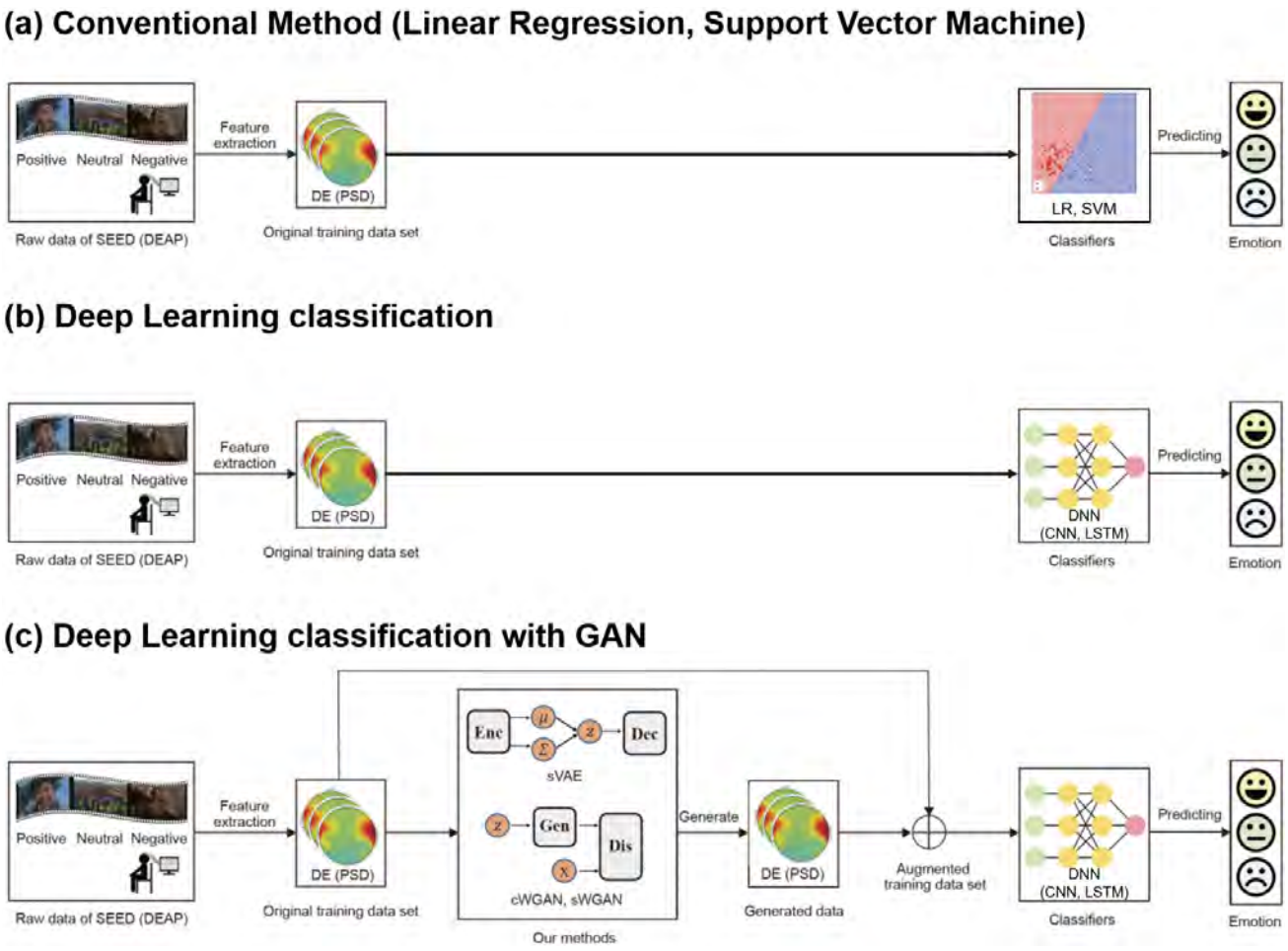

Figure 1 Concepts of classification methods in BCI. For emotion classification based on BCI signal, first, power spectral density (PSD), and differential entropy (DE) features are extracted from the EEG-based emotion recognition dataset. (a) Conventional method classifies emotions using a conventional classifier linear regression (LR) and support vector machine (SVM). (b) Deep learning methods include classifiers such as the convolutional neural network (CNN) and long short-term memory (LSTM). (c) Deep learning method is combined with a generative adversarial network (GAN). GAN generates realistic data and augments the original training dataset. Finally, the performance of BCI systems using SVM and DNN with shortcut layers is evaluated.

training datasets were augmented to generate a different number of realistic-like EEG data. Finally, SVM and deep neural networks (DNN) with short cut layers were trained to develop an effective model using the original and augmented training datasets. Therefore, augmented training datasets by sWGAN enhance the performance of EEG-based emotion recognition models from 83.3% to 92.2% (i.e., 10.2% improvement) and outperform existing data augmentation methods such as cWGAN (from 83.3% to 90.7%), sVAE (from 83.3% to 80.6%), Gaussian noise (from 83.3% to 85.8%), and rotational data augmentation (from 83.3% to 75.7%). Thus, augmentation based on GAN can improve BCI system performance while reducing the cost of acquiring EEG signal data and the effort of medical experts and patients.

Conclusion and Future Directions

This paper summarizes the developments made in brain-computer interfaces in the last decade to investigate the current trends in BCI research in the fields of medicine, communication, and control for clinical applications. We have summarized the challenges and limitations of the current BCI systems and proposed potential solutions. Numerous BCI systems have been developed, gradually progressing from a simple statistical model to a deep learning model, and consequently, BCI performance has improved over time. However, achieving a classification accuracy of > 90% via an online approach is still difficult. Thus, further development is required for implementing medical BCI systems on medicine settings. Furthermore, indi-

vidual BCI systems require training and parameter tuning for each task to be completed and they lack versatility. Considering the numerous clinical tasks to be achieved for clinical applications, developing a BCI system for each task is not feasible. To overcome this versatile problem, the Global Workspace Theory[35], which refers to a large-scale system integrating and distributing information among networks of specialized modules to create higher-level forms of cognition and awareness, has recently attracted considerable research attention, further advancing deep learning. Unsupervised neural translation between multiple latent spaces (neural networks trained for distinct tasks on distinct sensory inputs and/or modalities) to create a unique, amodal Global Latent Workspace can lead to improvement in the versatility and performance of BCI systems; this may be a promising theory in the medical BCI field[36].

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Author contributions

YS, KK, and RK conceived the presented idea. YS developed the theory and investigated the report on BCI system. KK and RK encouraged YS to investigate this work. All authors discussed the results and contributed to the final manuscript. Finally, all authors read and approved the final manuscript.

Conflicts of interest statement

RK is an employed at Araya Inc. (Tokyo, Japan). The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1) Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM: Brain-computer interfaces for communication and control. Clin Neurophysiol, 2002; 113: 767-791.
2) Miao Y, Chen S, Zhang X, *et al*: BCI-Based Rehabilitation on the Stroke in Sequela Stage. Neural Plast, 2020; 2020: 8882764.
3) Jin J, Chen Z, Xu R, Miao Y, Wang X, Jung TP: Developing a Novel Tactile P300 Brain-Computer Interface With a Cheeks-Stim Paradigm. IEEE Trans Biomed Eng, 2020; 67: 2585-2593.
4) Pan J, Xie Q, Qin P, *et al*: Prognosis for patients with cognitive motor dissociation identified by brain-computer interface. Brain, 2020; 143: 1177-1189.
5) Arpaia P, Esposito A, Natalizio A, Parvis M: How to successfully classify EEG in motor imagery BCI: a metrological analysis of the state of the art. J Neural Eng, 2022; 19: 031002.
6) Craik A, He Y, Contreras-Vidal JL: Deep learning for electroencephalogram (EEG) classification tasks: a review. J Neural Eng, 2019; 16: 031001.
7) Kübler A, Neumann N, Kaiser J, Kotchoubey B, Hinterberger T, Birbaumer NP: Brain-computer communication: self-regulation of slow cortical potentials for verbal communication. Arch Phys Med Rehabil, 2001; 82: 1533-1539.
8) Aravind M, Babu SS. Embedded implementation of brain computer interface using FPGA. 2016 International Conference on Emerging Technological Trends (ICETT), 2016; 1-5.
9) García PA, Spinelli EM, Toccaceli GM: An embedded system for evoked biopotential acquisition and processing. Int J Embed Syst, 2014; 6: 86-93.
10) Tseng KC, Lin BS, Wong AM, Lin BS: Design of a mobile brain computer interface-based smart multimedia controller. Sensors (Basel), 2015; 15: 5518-5530.
11) McCrimmon CM, Fu JL, Wang M, *et al*: Performance Assessment of a Custom, Portable, and Low-Cost Brain-Computer Interface Platform. IEEE Trans Biomed Eng, 2017; 64: 2313-2320.
12) Condori KA, Urquizo EC, Diaz DA: Embedded Brain Machine Interface based on motor imagery paradigm to control prosthetic hand. 2016 IEEE ANDESCON, 2016; 1-4.
13) Malekmohammadi A, Mohammadzade H, Chamanzar A, Shabany M, Ghojogh B: An efficient hardware implementation for a motor imagery brain computer interface system. Sci Iran, 2019; 26: 72-94.
14) Lawhern VJ, Solon AJ, Waytowich NR, Gordon SM, Hung CP, Lance BJ: EEGNet: a compact convolutional neural network for EEG-based brain-computer interfaces. J Neural Eng, 2018; 15: 056013.
15) Ma X, Zheng W, Peng Z, Yang J: FPGA-Based Rapid

Electroencephalography Signal Classification System. 2019 IEEE 11th International Conference on Advanced Infocomm Technology (ICAIT), 2019; 223–227.
16) Lou Q, Liu W, Liu W, Guo F, Jiang L. MindReading: An Ultra-Low-Power Photonic Accelerator for EEG-based Human Intention Recognition. 2020 25th Asia and South Pacific Design Automation Conference (ASP-DAC), 2020; 464–469.
17) Kwon OY, Lee MH, Guan C, Lee SW: Subject-Independent Brain-Computer Interfaces Based on Deep Convolutional Neural Networks. IEEE Trans Neural Netw Learn Syst, 2020; 31: 3839–3852.
18) Do AH, Wang PT, King CE, Schombs A, Cramer SC, Nenadic Z: Brain-computer interface controlled functional electrical stimulation device for foot drop due to stroke. Annu Int Conf IEEE Eng Med Biol Soc, 2012; 2012: 6414–6417.
19) Mao Y, Jin J, Li S, Miao Y, Cichocki A: Effects of Skin Friction on Tactile P300 Brain-Computer Interface Performance. Comput Intell Neurosci, 2021; 2021: 6694310.
20) İşcan Z, Nikulin VV: Steady state visual evoked potential (SSVEP) based brain-computer interface (BCI) performance under different perturbations. PLoS One, 2018; 13: e0191673.
21) Cho J, Lee K, Shin E, Choy G, Do S: How much data is needed to train a medical image deep learning system to achieve necessary high accuracy? https://doi.org/10.48550/arXiv.1511.06348 (Accessed Mar 20, 2023)
22) Lotte F, Bougrain L, Cichocki A, *et al*: A review of classification algorithms for EEG-based brain-computer interfaces: a 10 year update. J Neural Eng, 2018; 15: 031005.
23) Lotte F: Generating Artificial EEG Signals To Reduce BCI Calibration Time. 5th International Brain-Computer Interface Workshop, 2011; 176–179.
24) Lotte F: Signal Processing Approaches to Minimize or Suppress Calibration Time in Oscillatory Activity-Based Brain-Computer Interfaces. Proc IEEE, 2015; 103: 871–890.
25) Dinarès-Ferran J, Ortner R, Guger C, Solé-Casals J: A New Method to Generate Artificial Frames Using the Empirical Mode Decomposition for an EEG-Based Motor Imagery BCI. Front Neurosci, 2018; 12: 308.
26) Wang F, Zhong S-h, Peng J, Jiang J, Liu Y: Data Augmentation for EEG-Based Emotion Recognition with Deep Convolutional Neural Networks. In: Schoeffmann K, Chalidabhongse TH, Ngo CW, *et al*, eds. MultiMedia Modeling. Cham: Springer, 2018; 82–93.
27) Goodfellow IJ, Pouget-Abadie J, Mirza M, *et al*: Generative adversarial nets. In: Ghahramani Z, Welling M, Cortes C, Lawrence N, Weinberger KQ, eds. Advances in Neural Information Processing Systems 27. New York: Curran Associates, 2014; 2672–2680.
28) Reed S, Akata Z, Yan X, Logeswaran L, Schiele B, Lee H: Generative adversarial text to image synthesis. Proc Mach Learn Res, 2016; 48: 1060–1069.
29) Vondrick C, Pirsiavash H, Torralba A: Generating videos with scene dynamics. In: Lee D, Sugiyama M, Luxburg U, Guyon I, Garnett R, eds. Advances in Neural Information Processing Systems 29. New York: Curran Associates, 2016; 613–621.
30) Isola P, Zhu J-Y, Zhou T, Efros AA: Image-to-image translation with conditional adversarial networks. 2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), 2017; 5967–5976.
31) Roy S, Dora S, McCreadie K, Prasad G. MIEEG-GAN: Generating Artificial Motor Imagery Electroencephalography Signals. 2020 International Joint Conference on Neural Networks (IJCNN), 2020; 1–8.
32) Pascual D, Aminifar A, Atienza D, Ryvlin P, Wattenhofer R: Synthetic epileptic brain activities using generative adversarial networks. https://doi.org/10.48550/arXiv.1907.10518 (Accessed Mar 20, 2023)
33) Zhang Q, Liu Y: Improving brain computer interface performance by data augmentation with conditional deep convolutional generative adversarial networks. https://doi.org/10.48550/arXiv.1806.07108 (Accessed Mar 20, 2023)
34) Luo Y, Zhu LZ, Wan ZY, Lu BL: Data augmentation for enhancing EEG-based emotion recognition with deep generative models. J Neural Eng, 2020; 17: 056021.
35) Baars BJ: A cognitive theory of consciousness: Cambridge University Press, 1993.
36) VanRullen R, Kanai R: Deep learning and the Global Workspace Theory. Trends Neurosci, 2021; 44: 692–704.

Publication List

Juntendo Medical Journal
2023. 69(4), 327–348

Publications from Juntendo University Graduate School of Medicine, 2021 [2/6]

Cardiovascular Biology and Medicine

〈Original Articles〉

1) Fujiki S, Kashimura T, Okura Y, Kodera K, Watanabe H, Tanaka K, Bannai S, Hatano T, Tanaka T, Kitamura N, Minamino T, Inomata T: Incidence and Risk Factors of Future Need for Long-Term Care Insurance in Japanese Elderly Patients With Left Ventricular Systolic Dysfunction. Circ J, 2021 (in press).
2) Otsuki S, Izumi D, Sakaguchi Y, Suzuki N, Hakamata T, Ikami Y, Hasegawa Y, Yagihara N, Iijima K, Chinushi M, Minamino T, Takayuki I: Efficacy of antitachycardia pacing alert by remote monitoring of implantable cardioverter-defibrillators for out-of-hospital electrical storm. Pacing Clin Electrophysiol, 2021; 44: 1675–1682.
3) Fujiki S, Watanabe H, Obata H, Suda M, Mitsuma W, Tomii A, Sakai K, Uehara A, Shimizu I, Kashimura T, Ozaki K, Minamino T: Association of adipokines with frailty in heart failure. Acta Biomed, 2021; 92: e2021195.
4) Hasegawa Y, Izumi D, Ikami Y, Otsuki S, Yagihara N, Iijima K, Chinushi M, Minamino T: Progressive increase in activation delay during premature stimulation is related to ventricular fibrillation in Brugada syndrome. J Cardiovasc Electrophysiol, 2021; 32: 1939–1946.
5) Hagiya K, Ozaki K, Nanasato M, Iguchi N, Takayama M, Shimokawa T, Tanabe N, Minamino T, Isobe M: Relationship Between Heart Rate at Discharge and Long-Term Outcomes of Surgically Treated Patients With Type A Acute Aortic Dissections. Circ J, 2021; 85: 2191–2200.
6) Matsuo Y, Yoshimine F, Fuse K, Suzuki K, Sakamoto T, Iijima K, Ozaki K, Minamino T: Regional Disparities in Adherence to Guidelines for the Treatment of Chronic Heart Failure. Intern Med, 2021; 60: 525–532.
7) Hasegawa Y, Watanabe H, Ikami Y, Otsuki S, Iijima K, Yagihara N, Izumi D, Minamino T: J point elevation in high precordial leads associated with risk of ventricular fibrillation. Ann Noninvasive Electrocardiol, 2021; 26: e12820.
8) Matsuo S, Ozaki K, Matsuo Y, Takano T, Watanabe T, Sato T, Yagi T, Takayama T, Hoyano M, Yanagawa T, Ozawa T, Horii Y, Takano T, Kashimura T, Minamino T: Transcatheter coil embolization for large pulmonary arteriovenous fistulae through an artificial tricuspid ball valve. J Cardiol Cases, 2021; 25: 1–5.
9) Matsuo Y, Ozaki K, Ikegami R, Nishida K, Kubota N, Takano T, Okubo T, Hoyano M, Yanagawa T, Kashimura T, Minamino T: Conservative treatment with an intra-aortic balloon pump to treat acute myocardial infarction due to spontaneous coronary artery dissection. J Cardiol Cases, 2021; 23: 274–280.
10) Ozaki K, Okubo T, Hagiya K, Kubota N, Tsuchida K, Takahashi K, Oda H, Minamino T: Unstable angina complicated with dynamic left ventricular outflow tract obstruction. J Cardiol Cases, 2021; 23: 181–188.
11) Iso K, Nagashima K, Arai M, Watanabe R, Yokoyama K, Matsumoto N, Otsuka T, Suzuki S, Hirata A, Murakami M, Takami M, Kimura M, Fukaya H, Nakahara S, Kato T, Hayashi H, Iwasaki YK, Shimizu W, Nakajima I, Harada T, Koyama J, Okumura K, Tokuda M, Yamane T, Tanimoto K, Momiyama Y, Nonoguchi N, Soejima K, Ejima K, Hagiwara N, Harada M, Sonoda K, Inoue M, Kumagai K, Hayashi H, Yazaki Y, Satomi K, Watari Y, Okumura Y: AF Ablation Frontier Registry investigators. Clinical outcomes of ablation versus non-ablation therapy for atrial fibrillation in Japan: analysis of pooled data from the AF Frontier Ablation Registry and SAKURA AF Registry. Heart Vessels, 2021; 36: 549–560. doi: 10.1007/s00380-020-01721-x. Epub 2020 Nov 24
12) Minami-Takano A, Iwata H, Miyosawa K, Shiozawa T, Hayashi H, Funamizu T, Ishii K, Nozaki Y, Tabuchi H, Sekita G, Shimada K, Sumiyoshi M, Nakazato Y, Daida H, Minamino T: The association between impairment of HDL cholesterol efflux capacity and atrial remodeling in atrial fibrillation. Sci Rep, 2021; 11: 3547. doi: 10.1038/s41598-021-82998-4.
13) Akimoto S, Fukunaga H, Akiya A, Hosono Y, Iso T, Shigemitsu S, Tanaka N, Tabuchi H, Hayashi H, Sekita G, Takahashi K, Shimizu T: Deep insight into cardiac dysfunction in children and young adults with Wolff-Parkinson-White syndrome using speckle tracking imaging. Heart Vessels, 2021; 36: 1712–1720. doi: 10.1007/s00380-021-01848-5. Epub 2021 May 19.
14) Watanabe R, Nagashima K, Wakamatsu Y, Otsuka N, Yokoyama K, Matsumoto N, Otsuka T, Suzuki S, Hirata A, Murakami M, Takami M, Kimura M, Fukaya H, Nakahara S, Kato T, Hayashi H, Iwasaki

An asterisk (*) denotes doctoral works by Japanese students.
A dagger (†) denotes doctoral works by non-Japanese students.

YK, Shimizu W, Nakajima I, Harada T, Koyama J, Okumura K, Tokuda M, Yamane T, Tanimoto K, Momiyama Y, Nonoguchi N, Soejima K, Ejima K, Hagiwara N, Harada M, Sonoda K, Inoue M, Kumagai K, Hayashi H, Yazaki Y, Satomi K, Watari Y, Okumura Y; AF Ablation Frontier Registry Investigators: Different Determinants of the Recurrence of Atrial Fibrillation and Adverse Clinical Events in the Mid-Term Period After Atrial Fibrillation Ablation. Circ J. 2021. doi: 10.1253/circj.CJ-21-0326. Online ahead of print.

15) Usuda K, Kato T, Tsuda T, Tada H, Niwa S, Usui S, Sakata K, Hayashi K, Furusho H, Kawashiri M, Takamura M, Otsuka T, Suzuki S, Hirata A, Murakami M, Takami M, Kimura M, Fukaya H, Nakahara S, Shimizu W, Iwasaki YK, Hayashi H, Harada T, Nakajima I, Okumura K, Koyama J, Tokuda M, Yamane T, Momiyama Y, Tanimoto K, Soejima K, Nonoguchi N, Ejima K, Hagiwara N, Harada M, Sonoda K, Inoue M, Kumagai K, Hayashi H, Satomi K, Yazaki Y, Watari Y, Arai M, Watanabe R, Yokoyama K, Matsumoto N, Nagashima K, Okumura Y; on behalf of the AF Ablation Frontier Registry.Impact of sinus rhythm maintenance on major adverse cardiac and cerebrovascular events after catheter ablation of atrial fibrillation: insights from AF frontier ablation registry. Heart Vessels. 2021. doi: 10.1007/s00380-021-01929-5. Online ahead of print.
16) Shiozaki M, Sumiyoshi M, Tabuchi H, Hayashi H, Tamura H, Inoue K, Minamino T: A Case of J Wave Syndrome Due to Severe Hypercalcemia with Ventricular Fibrillation Storm and Successful Treatment of Isoproterenol Infusion. Int Heart J, 2021; 62: 924-926.
17) Masumoto A, Kitai T, Matsumoto S, Kuroda S, Kohsaka S, Tachikawa R, Seo R, Doi A, Tomii K,Yonetsu T, Torii S, Komuro I, Hirata KI, Node K, Matsue Y, Furukawa Y: Impact of serum lactate dehydrogenase on the short-term prognosis of COVID-19 with pre-existing cardiovascular diseases. J Cardiol, 2021; S0914-5087(21)00377-4.
18) Kuroda S, Matsumoto S, Sano T, Kitai T, Yonetsu T, Kohsaka S, Torii S, Kishi T, Komuro I, Hirata K, Node K, Matsue Y: External validation of the 4C mortality score for patients with COVID-19 and pre-existing cardiovascular diseases/risk factors. BMJ Open, 2021; 11: e052708.
19) Matsumoto S, Kuroda S, Sano T, Kitai T, Yonetsu T, Kohsaka S, Torii S, Kishi T, Komuro I, Hirata KI, Node K, Matsue Y: Clinical and Biomarker Profiles and Prognosis of Elderly Patients With Coronavirus Disease 2019 (COVID-19) With Cardiovascular Diseases and/or Risk Factors. Circ J, 2021; 85: 921-928. doi: 10.1253/circj.CJ-21-0160
20) Saito T, Yamaguchi T, Kuroda S, Kitai T, Yonetsu T, Kohsaka S, Torii S, Node K, Matsumoto S,Matsue Y, Kodama T: Impact of body mass index on the outcome of Japanese patients with cardiovascular diseases and/or risk factors hospitalized with COVID-19 infection. J Cardiol, 2021; S0914-5087.
21) Farwati M, Wazni OM, Tarakji KG, Diab M, Scandinaro A, Amin M, Zmaili M, Bazarbashi N,Dikilitas O, Nakagawa H, Kuroda S, Kanj M, Dresing TJ, Callahan TD, Bhargava M, Baranowski B, Rickard J, Cantillon DJ, Tchou PJ, Saliba WI, Hussein AA: Super and Nonresponders to Catheter Ablation for Atrial Fibrillation: A Quality-of-Life Assessment Using Patient Reported Outcomes. Circ Arrhythm Electrophysiol. 2021; 14: e009938.
22) Isogai T, Saad AM, Shekhar S, Kuroda S, Abushouk AI, Gad MM, Wazni OM, Krishnaswamy A, Kapadia SR: Incidence and Outcomes of Pericardial Effusion/Tamponade Following Percutaneous Left Atrial Appendage Closure. Am J Cardiol, 2021; 160: 126-129.
23) Isogai T, Agrawal A, Saad AM, Kuroda S, Shekhar S, Abushouk AI, Wazni OM, Hussein AA, Krishnaswamy A, Kapadia SR: Periprocedural and Short-Term Outcomes of Percutaneous Left Atrial Appendage Closure According to Type of Atrial Fibrillation. J Am Heart Assoc, 2021; 10: e022124.
24) Kuroda S, Wazni OM, Saliba WI, Hilow H, Baranowski B, Tarakji KG, Higuchi K, Tchou P, Dresing T, Lopez JO, Bhargava M, Cantillon DJ, Callahan T, Rickard J, Nakagawa H, Anter E, Hussein AA: The utility of a novel mapping algorithm utilizing vectors and global pattern of propagation for scar-related atrial tachycardias. J Cardiovasc Electrophysiol, 2021; 32: 909-997.
25) Nakagawa H, Kuroda S, Hussein AA: Radiofrequency ablation using a needle electrode combined with heated saline injection: Three different mechanisms of tissue heating. Heart Rhythm, 2021; 18: 453-454. doi: 10.1016/j.hrthm.2020.12.008.
26) Hayasaka K, Matsue Y, Kitai T, Okumura T, Kida K, Oishi S, Akiyama E, Suzuki S, Yamamoto M,Mizukami A, Yoshioka K, Kuroda S, Kagiyama N, Yamaguchi T, Sasano T: Tricuspid regurgitation pressure gradient identifies prognostically relevant worsening renal function in acute heart failure. Eur Heart J Cardiovasc Imaging, 2021; 22: 203-209.
27) Fukase T, Dohi T, Kato Y, Chikata Y, Takahashi N, Endo H, Doi S, Nishiyama H, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Daida H, Minamino T: Long-term clinical outcomes and cause of death after endovascular treatment for femoropopliteal artery lesions. J Cardiol, 2021; 77: 417-423.
28) Shimada K, Morinaga H, Kiyanagi T, Miyazaki T, Nishitani-Yokoyama M, Okai I, Tamura H, Konishi H, Kurata T, Miyauchi K, Daida H: Safety and Efficacy of Simultaneous Inoculations of Pneumococcal and Influenza Vaccines in Patients with Coronary Artery Disease. J Atheroscler Thromb, 2021; 28: 826-834.
29) Shitara J, Naito R, Kasai T, Endo H, Wada H, Doi S,

Konishi H, Tsuboi S, Ogita M, Dohi T, Okazaki S, Miyauchi K, Daida H: Differing effects of beta-blockers on long-term clinical outcomes following percutaneous coronary intervention between patients with mid-range and reduced left ventricular ejection fraction. BMC Cardiovasc Disord, 2021; 21: 36.

30) Kato Y, Dohi T, Chikata Y, Fukase T, Takeuchi M, Takahashi N, Endo H, Nishiyama H, Doi S, Okai I, Iwata H, Isoda K, Okazaki S, Miyauchi K, Daida H, Minamino T: Predictors of discordance between fractional flow reserve and resting full-cycle ratio in patients with coronary artery disease: Evidence from clinical practice. J Cardiol, 2021; 77: 313-319.

31) Nishio R, Ogita M, Wada H, Nozaki Y, Takahashi D, Yasuda K, Takeuchi M, Takahashi N, Sonoda T, Yatsu S, Shitara J, Tsuboi S, Dohi T, Suwa S, Miyauchi K, Daida H: Clinical Characteristics and Long-Term Outcomes of Patients with Acute Coronary Syndrome During Travel. Int Heart J, 2021; 62: 487-492.

32) Ueda R, Nishizaki Y, Nojiri S, Iwata H, Miyauchi K, Matsuyama K, Sanada S, Minamino T, Daida H: Factors Associated With the Acceleration of Patient Enrollment in Clinical Studies: A Cross-Sectional Study. Front Pharmacol, 2021; 12: 753067.

33) Takeuchi M, Wada H, Ogita M, Takahashi D, Okada-Nozaki Y, Nishio R, Yasuda K, Takahashi N, Sonoda T, Yatsu S, Shitara J, Tsuboi S, Dohi T, Suwa S, Miyauchi K, Daida H, Minamino T: Impact of Prior Stroke on Long-Term Outcomes in Patients With Acute Coronary Syndrome. Circ Rep, 2021; 3: 267-272.

34) Fukase T, Dohi T, Koike T, Yasuda H, Takeuchi M, Takahashi N, Chikata Y, Endo H, Doi S, Nishiyama H, Okai I, Iwata H, Okazaki S, Miyauchi K, Daida H, Minamino T: Long-term impact of β-blocker in elderly patients without myocardial infarction after percutaneous coronary intervention. ESC Heart Fail, 2021.

35) Fukase T, Dohi T, Kato Y, Chikata Y, Takahashi N, Endo H, Doi S, Nishiyama H, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Daida H, Minamino T: Long-term impact of high-sensitivity C-reactive protein in patients with intermittent claudication due to peripheral artery disease following endovascular treatment. Heart Vessels, 2021; 36: 1670-1678.

36) Takeuchi M, Dohi T, Takahashi N, Endo H, Doi S, Kato Y, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Minamino T: The prognostic implications of chronic kidney disease and anemia on long-term outcomes in patients undergoing percutaneous coronary intervention. Heart Vessels, 2021; 36: 1117-1124.

37) Fukase T, Dohi T, Chikata Y, Takahashi N, Endo H, Doi S, Nishiyama H, Kato Y, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Daida H, Minamino T: Serum apolipoprotein E levels predict residual cardiovascular risk in patients with chronic coronary syndrome undergoing first percutaneous coronary intervention and on-statin treatment. Atherosclerosis, 2021; 333: 9-15.

38) Takahashi N, Dohi T, Endo H, Takeuchi M, Doi S, Kato Y, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Minamino T: Coronary lipid-rich plaque characteristics in Japanese patients with acute coronary syndrome and stable angina: A near infrared spectroscopy and intravascular ultrasound study. Int J Cardiol Heart Vasc, 2021; 33: 100747.

39) Nishio R, Dohi T, Takeuchi M, Takahashi N, Endo H, Doi S, Okai I, Iwata H, Okazaki S, Miyauchi K, Daida H, Minamino T: Combined impact of residual inflammatory risk and chronic kidney disease on long-term clinical outcomes in patients undergoing percutaneous coronary intervention. J Cardiol, 2021: S0914-5087: 00301-4.

40) Abe M, Ozaki Y, Takahashi H, Ishii M, Masunaga N, Ismail TF, Iimuro S, Fujita R, Iwata H, Sakuma I, Nakagawa Y, Hibi K, Hiro T, Fukumoto Y, Hokimoto S, Miyauchi K, Ogawa H, Daida H, Shimokawa H, Saito Y, Matsuzaki M, Akao M, Kimura T, Nagai R: Relation of renal function to mid-term prognosis of stable angina patients with high- or low-dose pitavastatin treatment: REAL-CAD substudy. Am Heart J, 2021; 240: 89-100.

41) Noguchi M, Dohi T, Okazaki S, Matsumura M, Takeuchi M, Endo H, Kato Y, Okai I, Nishiyama H, Doi S, Iwata H, Isoda K, Usui E, Fujimura T, Seike F, Mintz GS, Miyauchi K, Daida H, Minamino T, Maehara A: Comparison of 6-month vascular healing response after bioresorbable polymer versus durable polymer drug-eluting stent implantation in patients with acute coronary syndromes: A randomized serial optical coherence tomography study. Catheter Cardiovasc Interv, 2021; 98: E677-E686.

42) Fukase T, Dohi T, Kato Y, Chikata Y, Takahashi N, Endo H, Doi S, Nishiyama H, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Daida H, Minamino T: High Apolipoprotein E Levels Predict Adverse Limb Events in Patients with Peripheral Artery Disease Due to Peripheral Artery Disease Undergoing Endovascular Treatment and On-Statin Treatment. Int Heart J, 2021; 62: 872-878.

43) Iwata H, Minamino T: Identification of a novel therapeutic target in vascular dysfunction: a showcase of reverse and forward translational research linking bench to bedside. Eur Heart J, 2021; ehab263.

44) Omote K, Yokota I, Nagai T, Sakuma I, Nakagawa Y, Kamiya K, Iwata H, Miyauchi K, Ozaki Y, Hibi K, Hiro T, Fukumoto Y, Mori H, Hokimoto S, Ohashi Y, Ohtsu H, Ogawa H, Daida H, Iimuro S, Shimokawa H, Saito Y, Kimura T, Matsuzaki M, Nagai R, Anzai T: REAL-CAD study investigators. High-Density Lipoprotein Cholesterol and Cardiovascular Events in Patients with Stable Coronary Artery Disease Treated with Statins: An Observation from the REAL-CAD Study. J Atheroscler Thromb, 2021.

45) Ishii J, Kashiwabara K, Ozaki Y, Takahashi H, Kitagawa F, Nishimura H, Ishii H, Iimuro S, Kawai H, Muramatsu T, Naruse H, Iwata H, Tanizawa-Motoyama S, Ito H, Watanabe E, Matsuyama Y, Fukumoto Y, Sakuma I, Nakagawa Y, Hibi K, Hiro T, Hokimoto S, Miyauchi K, Ohtsu H, Izawa H, Ogawa H, Daida H, Shimokawa H, Saito Y, Kimura T, Matsuzaki M, Nagai R: Small Dense Low-Density Lipoprotein Cholesterol and Cardiovascular Risk in Statin-Treated Patients with Coronary Artery Disease. J Atheroscler Thromb, 2021.

46) Iwata H, Osborn EA, Ughi GJ, Murakami K, Goettsch C, Hutcheson JD, Mauskapf A, Mattson PC, Libby P, Singh SA, Matamalas J, Aikawa E, Tearney GJ, Aikawa M, Jaffer FA: Highly Selective PPARα (Peroxisome Proliferator-Activated Receptor α) Agonist Pemafibrate Inhibits Stent Inflammation and Restenosis Assessed by Multimodality Molecular-Microstructural Imaging. J Am Heart Assoc, 2021; 10: e020834.

47) Aoshima C, Fujimoto S, Kawaguchi YO, Dohi T, Kamo Y, Takamura K, Hiki M, Kato Y, Okai I, Okazaki S, Kumamaru KK, Aoki S, Daida H: Plaque characteristics on coronary CT angiography associated with the positive findings of fractional flow reserve and instantaneous wave-free ratio. Heart Vessels, 2021; 36: 461-471.

48) Sunayama T, Matsue Y, Doi S, Okai I, Dohi T, Aoshima C, Miyazaki S, Hayashi H, Kasai T, Fujimoto S, Okazaki S, Shimada K, Daida H: Endomyocardial Biopsy for the Diagnosis of Transthyretin Cardiac Amyloidosis in the Era of Multimodality Imaging. Circ Rep, 2021; 3: 627-628.

49) Otsuki H, Jujo K, Tanaka K, Okai I, Nakashima M, Dohi T, Okazaki S, Okabe R, Nagura F, Nara Y, Kawashima H, Kyono H, Arashi H, Yamaguchi J, Tamura H, Kurata T, Miyauchi K, Kozuma K, Daida H, Hagiwara N: Sex differences in clinical outcomes after rotational atherectomy of calcified coronary stenoses: from multicenter registry. Am J Cardiovasc Dis, 2021; 11: 12-20.

50) Tomizawa N, Nozaki Y, Fujimoto S, Takahashi D, Kudo A, Kamo Y, Aoshima C, Kawaguchi Y, Takamura K, Hiki M, Dohi T, Okazaki S, Minamino T, Aoki S: A phantom and in vivo simulation of coronary flow to calculate fractional flow reserve using a mesh-free model. Int J Cardiovasc Imaging, 2021.

51) Kamo Y, Fujimoto S, Nozaki YO, Aoshima C, Kawaguchi YO, Dohi T, Kudo A, Takahashi D, Takamura K, Hiki M, Okai I, Okazaki S, Tomizawa N, Kumamaru KK, Aoki S, Minamino T: Incremental Diagnostic Value of CT Fractional Flow Reserve Using Subtraction Method in Patients with Severe Calcification: A Pilot Study. J Clin Med, 2021; 10: 4398.

52) Fukuda K, Okazaki S, Shiozaki M, Okai I, Nishino A, Tamura H, Inoue K, Sumiyoshi M, Daida H, Minamino T: Ultrasound-guided puncture reduces bleeding-associated complications, regardless of calcified plaque, after endovascular treatment of femoropopliteal lesions, especially using the antegrade procedure: A single-center study. PLoS One, 2021; 16: e0248416.

53) Takahashi N, Dohi T, Endo H, Okazaki S: Stepwise regression of non-culprit lipid-rich plaque observed using serial near-infrared spectroscopy-intravascular ultrasound and optical coherence tomographic measurements after aggressive cholesterol-lowering treatment: a case report. Eur Heart J Case Rep, 2021; 5: ytab095.

54) Nagasawa H, Ueda S, Otsuka T, Kaifu K, Ono S, Okuma T, Kobayashi T, Matsushita S, Kasai T, Dohi T, Fukushima Y, Amano A, Suzuki Y: Safety and efficacy of using cereal food (Frugra®) to improve blood pressure and bowel health in patients undergoing chronic hemodialysis: A pilot study. J Pharmacol Sci, 2021; 147: 132-137.

55) Sunayama T, Matsue Y*, Dotare T, Maeda D, Iso T, Morisawa T, Saitoh M, Yokoyama M, Jujo K, Takahashi T, Minamino T: Miltidomain frailty as a therapertic target in old patients with heart failure. Int Heart J, 2021; in-press.

56) Giang NM, Nguyen HH, Maeda D, Matsue Y: Tolvaptan add-on therapy to overcome loop Diuretic Resistance in Acute Heart Failure with renal dysfunction (DR-AHF): Design and Rationale. Front Cardiovasc Med, 2021; in-press.

57) Sano T, Matsumoto S, Kuroda S, Kitai T, Yonetsu T, Kohsaka S, Torii S, Node K, Matsue Y: New-Onset Atrial Fibrillation in Patients with COVID-19 and Cardiovascular Disease: Insights from the CLAVIS-COVID registry. Circ J, 2021; in-press.

58) Yatsu S, Kasai T, Naito R, Matsumoto H, Murata A, Shitara J, Shiroshita N, Kato M, Kawana F, Sato A, Ishiwata S, Shimizu M, Kato T, Suda S, Hiki M, Matsue Y, Kobayashi M, Yoshioka E, Yamauchi T, Daida H: Utility of cyclic variation of heart rate score as a screening tool for sleep-disordered breathing in patients with heart failure. J Clin Sleep Med, 2021; 17: 2187-2196.

59) Tanaka S, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Hamazaki N, Nozaki K, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Wakaume K, Oka K, Momomura SI, Kagiyama N, Matsue Y: Prevalence and prognostic value of the coexistence of anaemia and frailty in older patients with heart failure. ESC Heart Fail, 2021; 8: 625-633.

60) Nogi K, Ueda T, Matsue Y, Nogi M, Ishihara S, Nakada Y, Kawakami R, Kagiyama N, Kitai T, Oishi S, Akiyama E, Suzuki S, Yamamoto M, Kida K, Okumura T, Saito Y: Effect of carperitide on the 1-year prognosis of patients with acute decompensated heart failure. ESC Heart Fail, 2021; in-press.

61) Yamashita M, Kamiya K, Hamazaki N, Nozaki K,

Saito H, Saito K, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Wakaume K, Oka K, Momomura SI, Kagiyama N, Matsue Y: Work status before admission relates to prognosis in older patients with heart failure partly through social frailty. J Cardiol, 2021; in-press.

62) Emmans JE, ter Maaten JM, Matsue Y, Figarska SM, Sama IE, Cotter G, Cleland JGF, Davison BA, Felker GM, Givertz MM, Greenberg B, Pang PS, Severin T, Gimpelewicz C, Metra M, Voors AA, Teerlink JR: Worsening renal function in acute heart failure in the context of diuretic response. Eur J Heart Fail, 2021; in-press.

63) Saka K, Konishi M, Yamashita M, Kagiyama N, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Misumi T, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Makino A, Oka K, Kimura K, Tamura K, Momomura SI, Kagiyama N, Matsue Y: Impact of physical performance on exercise capacity in older patients with heart failure with reduced and preserved ejection fraction. Exp Gerontol, 2021; 156: 111626.

64) Maeda D, Matsue Y*, Kagiyama N, Jujo K, Saito K, Kamiya K, Saito H, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Wada H, Hiki M, Dotare T, Sunayama T, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Wakaume K, Oka K, Momomura SI, Minamino T: Sex differences in the prevalence and prognostic impact of physical frailty and sarcopenia among older patients with heart failure. Nutr Metab Cardiovasc Dis, 2021; in-press.

65) Yamada T, Ogawa T, Minami K, Kusaka Y, Masaaki H, Ukimura A, Sano T, Kitai T, Yonetsu T, Torii S, Kohsaka S, Kuroda S, Node K, Matsue Y, Matsumoto S: Multiple cardiovascular diseases or risk factors increase the severity of coronavirus disease 2019. Circ J, 2021; 85: 2111.

66) Kuroda S, Matsumoto S, Sano T, Kitai T, Yonetsu T, Kohsaka S, Torii S, Kishi T, Komuro I, Hirata K, Node K, Matsue Y*: External validation of the 4C mortality score for patients with COVID-19 and preexisting cardiovascular diseases/risk factors. BMJ Open, 2021; 11: e052708.

67) Kitakata H, Kohsaka S, Kuroda S, Nomura A, Kitai T, Yonetsu T, Torii S, Matsue Y, Matsumoto S: Inflammatory and Hypercoagulable Biomarkers and Clinical Outcomes in COVID-19 Patients. J Clin Med, 2021; 10: 3086.

68) Kitai T, Shimogai T, Wilson Tang WH, Iwata K, Xanthopoulos A, Otsuka S, Nakada F, Yokoyama R, Kamiya K, Saito H, Saito K, Maekawa E, Konishi M, Ogasawara Y, Jujo K, Wada H, Kasai K, Momomura S, Krittanawong C, Skoularigis J, Triposkiadis F, Kagiyama N, Furukawa Y, Matsue Y: Short physical performance battery vs. 6-minute walking test in hospitalized elderly patients with heart failure. Eur Heart J Open, 2021; in-press.

69) Matsue Y, Sama IE, Postmus D, Metra M, Greenberg B, Cotter G, Davison BA, Felker GM, Filippatos GS, Pang PS, Ponikowski P, Severin T, Gimpelewicz C, Voors AA, Teerlink JR: Association of early blood pressure decrease and renal function with prognosis in acute heart failure. JACC Heart Fail, 2021; 9: 890-903.

70) Sokolski M, Trenson S, Sokolska JM, D'Amario D, Meyer P, Poku NK, Biering-Sørensen T, Højbjerg Lassen MC, Skaarup KG, Barge-Caballero E, Pouleur AC, Stolfo D, Sinagra G, Ablasser K, Muster V, Rainer PP, Wallner M, Chiodini A, Heiniger PS, Mikulicic F, Schwaiger J, Winnik S, Cakmak HA, Gaudenzi M, Mapelli M, Mattavelli I, Paul M, Cabac-Pogorevici I, Bouleti C, Lilliu M, Minoia C, Dauw J, Costa J, Celik A, Mewton N, Montenegro CEL, Matsue Y, Loncar G, Marchel M, Bechlioulis A, Michalis L, Dörr M, Prihadi E, Schoenrath F, Messroghli DR, Mullens W, Lund LH, Rosano GMC, Ponikowski P, Ruschitzka F, Flammer AJ: Heart failure in COVID-19: the multicentre, multinational PCHF-COVICAV registry. ESC Heart Fail, 2021; in-press.

71) Shitara J, Kasai T, Murata N, Yamakawa N, Yatsu S, Murata A, Matsumoto H, Kato T, Suda S, Matsue Y, Naito R, Hiki M, Daida H: Temporal changes of cardiac acoustic biomarkers and cardiac function in acute decompensated heart failure. ESC Heart Fail, 2021; 8: 4037-4047

72) Ishiwata S, Matsue Y*, Nakamura Y, Dotare T, Sunayama T, Suda S, Yatsu S, Kato T, Hiki M, Kasai T, Minamino T: Clinical and prognostic values of urinary alpha1-microglobulin as a tubular marker in acute heart failure. Int J Cardiol, 2021; 338: 115-120.

73) Yoshida N, Iwata S, Ogawa M, Izawa KP, Kuroda S, Kohsaka S, Yonetsu T, Kitai T, Torii S, Sano T, Sakai Y, Yamashita T, Hirata K, Matsue Y, Matsumuto S, Node K: Intensive Care Unit Admission for Moderate-to-Severe COVID-19 Patients with Known Cardiovascular Disease or Their Risk Factors. Circ Rep, 2021; in-press

74) Kida K, Kitai T, Suzuki N, Ashikaga K, Kou S, Kagiyama N, Yamaguchi T, Okumura T, Mizuno A, Oishi S, Inuzuka Y, Akiyama E, Suzuki S, Yamamoto M, Matsue Y*: Prognostic Implications of Reduction in Heart Rates in Patients with Acute Heart Failure and Atrial Fibrillation. Circ J, 2021; 85: 1869-1875.

75) Jujo K, Kagiyama N, Saito K, Kamiya K, Saito H, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Yonezawa R, Oka K, Makizako H, Momomura SI, Matsue Y*: Impact of social frailty in hospitalized elderly patients with heart failure: A FRAGILE-HF registry subanalysis. J Am Heart Assoc, 2021; 10: e019954.

76) Ozawa T, Yamashita M, Seino S, Kamiya K, Kagiyama N, Konishi M, Saito H, Saito K, Ogasahara Y, Maekawa E, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Momomura SI, Hamazaki N, Nozaki K, Kim HK, Obuchi S, Kawai H, Kitamura A, Shinkai S, Matsue Y*: Standardized gait speed ratio in elderly patients with heart failure. ESC Heart Fail, 2021; 8: 3557–3565.
77) Hiki M, Tabe Y, Ai T, Matsue Y, Harada N, Sugimoto K, Matsushita Y, Matsushita M, Wakita M, Misawa S, Idei M, Miida T, Takahashi K, Naito T: Seroprevalence of anti-SARS-CoV-2 antibodies in Japanese COVID-19 patients. PLoS One, 2021; 16: e0249449.
78) Kagiyama N, Hiki M, Matsue Y, Dohi T, Matsuzawa W, Diada H, Minamino T, Kasai T: Validation of Telemedicine-based Self-Assessment of Vital Signs for Patients with COVID-19: A Pilot Study. J Telemed Telecare, 2021; in-press.
79) Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Felker GM, Filippatos G, Fonarow GC, Fiuzat M, Gomez-Mesa JE, Heidenreich P, Imamura T, Januzzi J, Jankowska EA, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, SeferoviĆ P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S: Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail, 2021; 27: 387–413.
80) Ikari Y, Matsue Y, Torii S, Hasegawa M, Aihara K, Kuroda S, Sano T, Kitai T, Yonetsu T, Kohsaka S, Kishi T, Komuro I, Hirata KI, Node K, Matsumoto S: Association Between Statin Use Prior to Admission and Lower Coronavirus Disease 2019 (COVID-19) Severity in Patients With Cardiovascular Disease or Risk Factors. Circ J, 2021; 85: 939.
81) Hirose S, Matsue Y, Kamiya K, Kagiyama N, Hiki M, Dotare T, Sunayama T, Konishi M, Saito H, Saito K, Ogasahara Y, Maekawa E, Kitai T, Jujo K, Wada H, Kasai T, Momomura SI, Minamino T: Prevalence and prognostic implications of malnutrition as defined by GLIM criteria in elderly patients with heart failure. Clin Nutr, 2021; 40: 4334–4340.
82) Kohei N, Kamiya K, Hamazaki N, Siato H, Saito K, Ogasahara Y, Maekara E, Konishi M, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Yonezawa R, Oka K, Momomura S-I, Kagiyama N, Matsue Y: Validity and utility of the questionnaire-based FRAIL scale in elderly patients with heart failure: Findings from the FRAGILE-HF. J Am Med Dir Assoc, 2021; 42: 3031–3031.
83) Kato T, Kasai T, Suda S, Sato A, Ishiwata S, Yatsu S, Matsumoto H, Shitara J, Shimizu M, Murata A, Kagiyama N, Hiki M, Matsue Y, Naito R, Takagi A, Daida H: Prognostic effects of arterial carbon dioxide levels in patients hospitalized into the cardiac intensive care unit for acute heart failure. Eur Heart J Acute Cardiovasc Care, 2021; 10: 497–502.
84) Sahashi Y, Endo H, Sugimoto T, Nabeta T, Nishizaki K, Kikuchi A, Matsumoto S, Sato H, Goto T, Hasegawa K, Matsue Y: Worries and concerns among healthcare workers during the coronavirus 2019 pandemic: A web-based cross-sectional survey. Humanit Soc Sci Commun, 2021; 8: 41.
85) Hayasaka K†, Matsue Y*†, Kitai T, Okumura T, Kida K, Oishi S, Akiyama E, Suzuki S, Yamamoto M, Mizukami A, Yoshioka K, Kuroda S, Kagiyama N, Yamaguchi T, Sasano T: Tricuspid regurgitation pressure gradient identifies prognostically relevant worsening renal function in acute heart failure. (†equally contributed) Eur Heart J, 2021; 22: 203–209.
86) Ishiwata S, Kato T, Kasai T, Sato A, Yatsu S, Matsumoto H, Shitara J, Murata A, Shimizu M, Suda S, Matsue Y, Naito R, Hiki M, Daida H: Changes in self-reported physical activity and health-related quality of life following 3-month astaxantin supplementation in patients with heart failure: results from a pilot study. Ann Palliat Med, 2021; 10: 1396–1403.
87) Konishi M, Kagiyama N, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Misumi T, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Makino A, Oka K, Momomura SI, Matsue Y: Impact of sarcopenia on prognosis in patients with heart failure with reduced and preserved ejection fraction. Eur J Prev Cardiol, 2021; 28: 1022–1029.
88) Sato A, Kato T, Kasai T, Ishiwata S, Yatsu S, Matsumoto H, Shitara J, Murata A, Shimizu M, Suda S, Matsue Y, Naito R, Hiki M, Diada H: Relationship between inflammatory biomarkers and sleep-disordered breathing in patients with heart failure Sleep Biol Rhythm. Sleep Biol Rhythm, 2021; 19: 55–61.
89) Ito M, Matsue Y*, Minamino T: Worsening renal function during intensive blood pressure control: another example of not prognostically relevant creatinine rise? Eur J Heart Fail, 2021; 23: 384–392.
90) Yamamoto H, Kihara Y, Fujimoto S, Daida H, Kobuke K, Iwanaga Y, Miyazaki S, Kawasaki T, Fujii T, Kuribayashi S: Predictive value of the coronary artery calcium score and advanced plaque characteristics: Post hoc analysis of the PREDICT registry. J Cardiovasc Comput Tomogr, 2021; 5: 148–153.
91) Einstein AJ, Shaw LJ, Hirschfeld C, Williams MC, Villines TC, Better N, Vitola JV, Cerci R, Dorbala S, Raggi P, Choi AD, Lu B, Sinitsyn V, Sergienko V, Kudo T, Nørgaard BL, Maurovich-Horvat P, Campisi R, Milan E, Louw L, Allam AH, Bhatia M, Malkovskiy

E, Goebel B, Cohen Y, Randazzo M, Narula J, Pascual TNB, Pynda Y, Dondi M, Paez D; INCAPS COVID Investigators Group: International Impact of COVID-19 on the Diagnosis of Heart Disease. J Am Coll Cardiol, 2021; 77: 173-185.

92) Hirschfeld CB, Shaw LJ, Williams MC, Lahey R, Villines TC, Dorbala S, Choi AD, Shah NR, Bluemke DA, Berman DS, Blankstein R, Ferencik M, Narula J, Winchester D, Malkovskiy E, Goebel B, Randazzo MJ, Lopez-Mattei J, Parwani P, Vitola JV, Cerci RJ, Better N, Raggi P, Lu B, Sergienko V, Sinitsyn V, Kudo T, Nørgaard BL, Maurovich-Horvat P, Cohen YA, Pascual TNB, Pynda Y, Dondi M, Paez D, Einstein AJ; INCAPS-COVID Investigators Group: Impact of COVID-19 on Cardiovascular Testing in the United States Versus the Rest of the World: The INCAPS-COVID Study. JACC Cardiovasc Imaging, 2021; S1936-878X(21)00265-5.

93) Nozaki YO, Fujimoto S, Aoshima C, Kamo Y, Kawaguchi YO, Takamura K, Kudo A, Takahashi D, Hiki M, Kato Y, Okai I, Dohi T, Okazaki S, Tomizawa N, Kumamaru KK, Aoki S, Minamino T: Comparison of diagnostic performance in on-site based CT-derived fractional flow reserve measurements. Int J Cardiol Heart Vasc, 2021; 35: 100815. doi: 10.1016/j.ijcha.2021.100815.

94) Fujimoto S: Development of Comprehensive Coronary Assessment Using Coronary Computed Tomography Angiography - Possibility of Novel Imaging Markers for Coronary Inflammation - Int J Cardiol, 2021; 58: 272-278.

95) Kudo T, Lahey R, Hirschfeld C ; INCAPS-COVID Investigators Group: Impact of COVID-19 Pandemic on Cardiovascular Testing in Asia: The IAEA INCAPS-COVID Study. JACC: Asia, 2021; 1: 200-202.

96) Thavendiranathan P, Negishi T, Somerset E, Negishi K, Penicka M, Lemieux J, Aakhus S, Miyazaki S, Shirazi M, Galderisi M, Marwick TH; SUCCOUR Investigators: Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol, 2021; 77: 392-401.

97) Onishi T, Fukuda Y, Miyazaki S, Yamada H, Tanaka H, Sakamoto J, Daimon M, Izumi C, Nonaka A, Nakatani S, Akaishi M; Guideline Committee of the Japanese Society of Echocardiography: Practical guidance for echocardiography for cancer therapeutics-related cardiac dysfunction. J Echocardiogr, 2021; 19: 1-20.

98) Kaneko T, Kagiyama N, Nakamura Y, Hirasawa T, Murata A, Morimoto R, Miyazaki S, Minamino T: Effectiveness of real-time tele-ultrasound for echocardiography in resource-limited medical teams. J Echocardiogr, 2021; 1-8.

99) Kaneko T, Miyazaki S, Koike T, Murata A, Morimoto R, Hirose K, Takamura K, Endo D, Amano A, Minamino T: A Case of Atypical Shone's Complex Diagnosed at 70 Years Old: Presenting with Double-orifice Mitral Valve, Bicuspid Aortic Valve, and Aortic Coarctation. Intern Med, 2021.

100) Ito M, Horimoto Y, Sasaki R, Miyazaki S, Orihata G, Saito M: Cardiotoxicity after Additional Administration of Pertuzumab following Long-Term Trastuzumab: Report of 2 Cases. Case Rep Oncol, 2021; 14: 62-66.

101) Kagiyama N, **Pandey A, Yanamala N, Segar MW, Cho JS, Tokodi M, Sengupta PP: Deep-learning models for the echocardiographic assessment of diastolic dysfunction. JACC Cardiovasc Imaging, 2021; 14: 1887-1900 (** double first authors)

102) Kagiyama N, Toki M, Yuri T, Aritaka S, Hayashida A, Sengupta PP, Yoshida K: Physiological and prognostic differences between types of exercise stress echocardiography for functional mitral regurgitation. Open Heart, 2021; 8.

103) Sengupta PP, Shrestha S, Kagiyama N, Hamirani Y, Kulkarni H, Yanamala N, Bing R, Chin CWL, Pawade TA, Messika-Zeitoun D, Tastet L, Shen M, Newby DE, Clavel MA, Pibarot P, Dweck MR: A machine-learning framework to identify distinct phenotypes of aortic stenosis severity. JACC Cardiovasc Imaging, 2021; 14: 1707-1720.

104) Hasselberg NE, Kagiyama N, Soyama Y, Sugahara M, Goda A, Ryo-Koriyama K, Batel O, Chakinala M, Simon MA, Gorcsan J, 3rd: The prognostic value of right atrial strain imaging in patients with precapillary pulmonary hypertension. J Am Soc Echocardiogr, 2021; 34: 851-861 e851.

105) Ishida M, Matsumoto C, Kida K, Fukuda M, Kagiyama N, Kusunose K, Matsumoto S, Nomura S, Okumura T, Shiono Y, Taniguchi T, Mizuno A, Kishi T, Node K, Komuro I, Hirata KI: New vision, mission, and values of the Japanese Circulation Society. Circ J, 2021; 85: 2248-2251.

106) Skov Schacksen C, Henneberg NC, Muthulingam JA, Morimoto Y, Sawa R, Saitoh M, Morisawa T, Kagiyama N, Takahashi T, Kasai T, Daida H, Refsgaard J, Hollingdal M, Dinesen B: Effects of telerehabilitation interventions on heart failure management (2015-2020): Scoping review. JMIR Rehabil Assist Technol, 2021; 8: e29714.

107) Kunimoto M, Yokoyama M, Shimada K, Matsubara T, Aikawa T, Ouchi S, Fukao K, Miyazaki T, Fujiwara K, Abulimiti A, Honzawa A, Shimada A, Yamamoto T, Amano A, Saitoh M, Morisawa T, Takahashi T, Daida H, Minamino T: Relationship between skin autofluorescence levels and clinical events in patients with heart failure undergoing cardiac rehabilitation. Cardiovasc Diabetol, 2021; 20: 208.

108) Morisawa T, Saitoh M, Takahashi T, Watanabe H, Mochizuki M, Kitahata E, Fujiwara T, Fujiwara K, Yokoyama M, Minamino T, Shimada K, Honzawa A, Shimada A, Yamamoto T, Asai T, Amano A, Daida H: Association of phase angle with hospital-acquired

functional decline in older patients undergoing cardiovascular surgery. Nutrition, 2021; 91–92: 111402.

109) Yokoyama M, Shimada K, Yamada M, Honzawa A, Kunimoto M, Sugita Y, Fujiwara, K, Matsubara T, Matsumori R, Abulimiti A, Shimada A, Yamamoto T, Asai T, Amano A, Saitoh M,Morisawa T, Takahashi T, Daida H, Minamino T: Association between Constipation and Frailty Components in Patients Undergoing Late Phase II Cardiac Rehabilitation. Cardiol Res, 2021; 12: 169–176.

110) Kida K, Yokoyama M, Oishi S, Kono Y, Kamiya K, Kishi T, Node K, Makita S, Kimura Y: A Nationwide Survey of Japanese Cardiac Rehabilitation Training Facilities Under Coronavirus Disease 2019 Outbreak. Circ Rep, 2021; 3: 311–315.

111) Abulimiti A*, Yokoyama M, Shimada K, Kunimoto M, Matsubara T, Fujiwara K, Aikawa T, Ouchi S, Sugita Y, Fukao K, Kadoguchi T, Miyazaki T, Shimada A, Yamamoto T, Takahashi T, Fujiwara T, Asai T, Amano A, Daida H, Minamino T: Prognostic impact of peak oxygen uptake and heart rate reserve in patients after off-pump coronary artery bypass grafting. Clinical Cardiology, 2021; 44: 580–587. *Abulimiti A. and Yokoyama M. contributed equally to this work.

112) Fujiwara K, Shimada K, Nishitani-Yokoyama M, Kunimoto M, Matsubara T, Matsumori R, Abulimiti A, Aikawa T, Ouchi S, Shimizu M, Fukao K, Miyazaki T, Honzawa A, Yamada M, Saito M, Morisawa T, Takahashi T, Daida H, Minamino T: Arterial stiffness index and exercise tolerance in patients undergoing cardiac rehabilitation: comparison between patients with preserved and reduced ejection fraction. Int Heart J, 2021; 62: 230–237.

113) Takahashi T, Morisawa T, Saitoh M, Honzawa A, Abulimiti A, Fujihara K, Yokoyama M, Shimada K, Minamino T, Fujihara T, Daida H: Forefront of Cardiac Rehabilitation in Japan. Juntendo Medical Journal, 2021; 67–1.

114) Hsiao YT*, Shimizu I*,**, Wakasugi T, Jiao S, Watanabe T, Yoshida Y, Ikegami R, Hayashi Y, Suda M, Katsuumi G, Nakao M, Ozawa T, Kashimura T, Ozaki K, Hanawa H, Minamino T**: Cardiac Mitofusin-1 is Reduced in Non-responding Patients with Idiopathic Dilated Cardiomyopathy. Sci Rep, 2021; 11: 6722. *Co-first author, **Co-corresponding author

115) Nakao M*, Shimizu I*,**, Katsuumi G, Yoshida Y, Suda M, Hayashi Y, Ikegami R, Hsiao Yung Ting, Okuda S, Soga T, Minamino T**: Empagliflozin Maintains Capillarization and Improves Cardiac Function in a Murine Model of Left Ventricular Pressure Overload. Sci Rep, 2021; 11: 18384 (2021). *Co-first author, **Co-corresponding author

116) Cho K, Ushiki T, Ishiguro H Tamura S, Araki M, Suwabe T, Katagiri T, Ohashi R, Ajioka Y, Shimizu I, Okuda S, Masuko M, Nakagawa Y, Hirai H, Alexander W, Shimano H, Sone H: Altered Microbiota by a High-Fat Diet Accelerates Lethal Myeloid Hematopoiesis Associated with Systemic Socs3 Deficiency. iScience, 2021; 24: 103117.

117) Furihata T, Takada S, Kakutani N, Maekawa S, Tsuda M, Matsumoto J, Mizushima W, Fukushima A, Yokota T, Enzan N, Matsushima S, Handa H, Fumoto Y, Nio-Kobayashi J, Iwanaga T, Tanaka S, Tsutsui H, Sabe H, Kinugawa S: Cardiac-specific loss of mitoNEET expression is linked with age-related heart failure. Commun Biol, 2021; 4: 138.

118) Furihata T, Maekawa S, Takada S, Kakutani N, Nambu H, Shirakawa R, Yokota T, Kinugawa S: Premedication with pioglitazone prevents doxorubicin-induced left ventricular dysfunction in mice. BMC Pharmacol Toxicol, 2021; 22: 27.

119) Matsumoto J, Takada S, Furihata T, Nambu H, Kakutani N, Maekawa S, Mizushima W, Nakano I, Fukushima A, Yokota T, Tanaka S, Handa H, Sabe H, Kinugawa S: Brain-Derived Neurotrophic Factor Improves Impaired Fatty Acid Oxidation Via the Activation of Adenosine Monophosphate-Activated Protein Kinase-a – Proliferator-Activated Receptor-r Coactivator-1a Signaling in Skeletal Muscle of Mice With Heart Failure. Circ Heart Fail, 2021; 14: e005890.

120) Nambu H, Takada S, Maekawa S, Matsumoto J, Kakutani N, Furihata T, Shirakawa R, Katayama T, Nakajima T, Yamanashi K, Obata Y, Nakano I, Tsuda M, Saito A, Fukushima A, Yokota T, Nio-Kobayashi J, Yasui H, Higashikawa K, Kuge Y, Anzai T, Sabe H, Kinugawa S: Inhibition of xanthine oxidase in the acute phase of myocardial infarction prevents skeletal muscle abnormalities and exercise intolerance. Cardiovasc Res, 2021; 117: 805–819.

121) Kakutani N, Takada S, Nambu H, Maekawa S, Hagiwara H, Yamanashi K, Obata Y, Nakano I, Fumoto Y, Hata S, Furihata T, Fukushima A, Yokota T, Kinugawa S: Angiotensin-converting enzyme inhibitor prevents skeletal muscle fibrosis in diabetic mice. Exp Physiol, 2021; 106: 1785–1793.

122) Suda M*, Shimizu I*, Katsuumi G*, Yoshida Y, Hayashi Y, Ikegami R, Matsumoto N, Yoshida Y, Mikawa R, Katayama A, Wada J, Seki M, Suzuki Y, Iwama A, Nakagami H, Nagasawa A, Morishita R, Sugimoto M, Okuda S, Tsuchida M, Ozaki K, Nakanishi-Matsui M, Minamino T: Senolytic vaccination improves normal and pathological age-related phenotypes and increases lifespan in progeroid mice. Nat Aging, 2021; 1: 1117–1126. *Co-first author

123) Joki Y, Konishi H, Ebinuma H, Takasu K, Minamino T: Circulating sLR11 levels predict severity of pulmonary hypertension due to left heart disease. PLoS One, 2021; 16: e0261753. doi: 10.1371/journal.pone.0261753.

124) Sai E, Shimada K, Aikawa T, Aoshima C, Takamura K, Hiki M, Yokoyama T, Miyazaki T, Fujmoto S, Konishi

H, Hirano KI, Daida H, Minamino T: Triglyceride Deposit Cardiomyovasculopathy with Massive Myocardial Triglyceride which Was Proven Using Proton-magnetic Resonance Spectroscopy. Intern Med, 2021; 60: 1217-1220.

125) Shimada K, Morinaga H, Kiyanagi T, Miyazaki T, Nishitani-Yokoyama M, Okai I, Tamura H, Konishi H, Kurata T, Miyauchi K, Daida H: Safety and Efficacy of Simultaneous Inoculations of Pneumococcal and Influenza Vaccines in Patients with Coronary Artery Disease. J Atheroscler Thromb, 2021; 28: 826-834.

126) Sata N, Inoshita A, Suda S, Shiota S, Shiroshita N, Kawana F, Suzuki Y, Matsumoto F, Ikeda K, Kasai T: Clinical, polysomnographic, and cephalometric features of obstructive sleep apnea with AHI over 100. Sleep Breath, 2021; 25: 1379-1387.

127) Uchida T, Nishimura A, Kasai T, Kikuno S, Nagasawa K, Okubo M, Narui K, Mori Y: Relationship between obstructive sleep apnoea during rapid eye movement sleep and metabolic syndrome parameters in patients with type 2 diabetes mellitus. Sleep Breath, 2021; 25: 309-314.

128) Sato A, Naito R, Kasai T: Screening for Sleep Apnea in Atrial Fibrillation Prior to Catheter Ablation. Circ J, 2021; 85: 261-263.

129) Kasai T, Peker Y: To Salt or Not to Salt? - Is That a Question in Obstructive Sleep Apnea? Ann Am Thorac Soc, 2021; 18: 424-425.

130) Naito R, Leong DP, Bangdiwala SI, McKee M, Subramanian SV, Rangarajan S, Islam S, Avezum A, Yeates KE, Lear SA, Gupta R, Yusufali A, Dans AL, Szuba A, Alhabib KF, Kaur M, Rahman O, Seron P, Diaz R, Puoane T, Liu W, Zhu Y, Sheng Y, Lopez-Jaramillo P, Chifamba J, Rosnah I, Karsidag K, Kelishadi R, Rosengren A, Khatib R, K R LIA, Azam SI, Teo K, Yusuf S: Impact of social isolation on mortality and morbidity in 20 high-income, middle-income and low-income countries in five continents. BMJ Glob Health, 2021; 6: e004124. PMID: 33753400

131) Kario K, Nishizawa M, Kiuchi M, Kiyosue A, Tomita F, Ohtani H, Abe Y, Kuga H, Miyazaki S, Kasai T, Hongou M, Yasu T, Kuramochi J, Fukumoto Y, Hoshide S, Hisatome I: Comparative effects of topiroxostat and febuxostat on arterial properties in hypertensive patients with hyperuricemia. J Clin Hypertens (Greenwich), 2021; 23: 334-344.

132) Nishimura A, Kasai T, Matsumura K, Kikuno S, Nagasawa K, Okubo M, Narui K, Mori Y: Sleep disordered breathing during rapid eye movement sleep and diabetic kidney disease in patients with type 2 diabetes. J Clin Sleep Med, 2021; 17: 453-460.

133) Maeda D, Kagiyama N, Jujo K, Saito K, Kamiya K, Saito H, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Wada H, Hiki M, Dotare T, Sunayama T, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Yonezawa R, Oka K, Momomura SI, Matsue Y: Aspartate aminotransferase to alanine aminotransferase ratio is associated with frailty and mortality in older patients with heart failure. Sci Rep, 2021; 11: 11957.

134) Nozaki K, Kamiya K, Hamazaki N, Saito H, Saito K, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Yonezawa R, Oka K, Momomura S, Kagiyama N, Matsue Y: Validity and utility of the questionnaire-based FRAIL scale in elderly patients with heart failure: Findings from the FRAGILE-HF. J Am Med Dir Assoc, 2021; 22: 1621-1626. e2.

135) Yatsu S, Kasai T*, Naito R, Matsumoto H, Murata A, Shitara J, Shiroshita N, Kato M, Kawana F, Sato A, Ishiwata S, Shimizu M, Kato T, Suda S, Hiki M, Matsue Y, Kobayashi M, Yoshioka E, Yamauchi T, Daida H: Utility of cyclic variation of heart rate score as a screening tool for sleep-disordered breathing in patients with heart failure. J Clin Sleep Med, 2021; 17: 2187-2196. PMID:34013882

136) Neeland IJ, Kasai T, Inzucchi SE, Wojeck BS, Yaggi HK, Johansen OE; EMPA-REG OUTCOME Investigators: The Impact of Empagliflozin on Obstructive Sleep Apnea and Cardiovascular and Renal Outcomes: An Exploratory Analysis of the EMPA-REG OUTCOME Trial. Diabetes Care, 2020; 43: 3007-3015. Diabetes Care, 2021; 44: e137-8.

137) Inoshita A, Matsumoto F, Ohba S, Sata N, Matsuoka R, Suzuki Y, Ito S, Koiwai H, Shiroshita N, Kasai T, Ikeda K: Severe obstructive sleep apnea after concurrent chemoradiotherapy for laryngeal and hypopharyngeal cancer. Auris Nasus Larynx, 2021. [Online ahead of print]

138) Imanari S, Tomita Y, Kasagi S, Kawana F, Kimura Y, Ishiwata S, Narui K, Kasai T: Evaluation of the apnea-hypopnea index determined by adaptive servo-ventilation devices in patients with heart failure and sleep-disordered breathing. Front Cardiovasc Med, 2021; 8: 680053.

139) Saito T, Nojiri S, Naito R, Daida H, Kasai T*: Regional variations in the utilization of adaptive servo ventilation and continuous positive airway pressure in Japan—Data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) Open Data Japan. Sleep Biol Rhythms, 2021; 19: 409-422.

140) Tobushi T, Kasai T, Hirose M, Sakai K, Akamatsu M, Ohsawa C, Yoshioka Y, Suda S, Shiroshita N, Nakamura R, Kadokami T, Tohyama T, Funakoshi K, Hosokawa K, Ando SI: Lung-to-finger circulation time can be measured stably with high reproducibility by simple breath holding method in cardiac patients. Sci Rep, 2021; 11: 15913.

141) Naito R, Kasai T: Sodium glucose cotransporter 2 inhibitors -New horizon of the heart failure pharma-

cotherapy. World J Cardiol, 2021; 13: 464–471.PMID: 34621491

142) Naito R, Kasai T: Bereavement of a child as a risk of heart failure. Eur J Heart Fail, 2021. Online ahead of print. PMID: 34816534

143) Kitamura E, Kawasaki Y, Kasai T*, Midorikawa I, Shiroshita N, Kawana F, Ogasawara E, Kitade M, Itakura A, Koikawa N, Matsuda T: The relationship between body composition and sleep architecture in athletes. Sleep Med, 2021 In press.

144) Yamashita M, Kamiya K, Hamazaki N, Saito H, Saito K, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Wakaume K, Oka K, Momomura SI, Kagiyama N, Matsue Y: Work status before admission relates to prognosis in older patients with heart failure partly through social frailty. J Cardiol, 2021. Online ahead of print. PMID: 34819268

145) Saka K, Konishi M, Kagiyama N, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, Misumi T, Kitai T, Iwata K, Jujo K, Wada H, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Makino A, Oka K, Kimura K, Tamura K, Momomura SI, Matsue Y: Impact of physical performance on exercise capacity in older patients with heart failure with reduced and preserved ejection fraction. Exp Gerontol, 2021; 156: 111626.

146) Dotare T, Ishiwata S, Matsue Y, Nakamura Y, Maeda D, Yatsu S, Suda S, Kato T, Hiki M, Kasai T, Minamino T: Prevalence and Prognostic Relevance of Isolated Tubular Dysfunction in Patients With Acute Heart Failure. Circ J, 2021. Online ahead of print. PMID: 34955476

147) Shimai R, Ouchi S, Miyazaki T, Hirabayashi K, Abe H, Yabe K, Maki M, Isogai H, Wada T, Ozaki D, Odagiri F, Hiki M, Yaginuma K, Yokoyama K, Tokano T, Minamino T: A case of ST-elevation acute myocardial infarction in a nonhospitalized patient with SARS-CoV-2 pneumonia: Treatment with Primary Percutaneous Coronary Intervention. Clin Case Rep, 2021; 9: e04785.

148) Abulimiti A, Nishitani-Yokoyama M, Shimada K, Kunimoto M, Matsubara T, Fujiwara K, Aikawa T, Ouchi S, Sugita Y, Fukao K, Kadoguchi T, Miyazaki T, Shimada A, Yamamoto T, Takahashi T, Fujiwara T, Asai T, Amano A, Daida H, Minamino T: Prognostic impact of peak oxygen uptake and heart rate reserve in patients after off-pump coronary artery bypass grafting. Clin Cardiol, 2021; 44: 580–587.

149) Sai E, Shimada K, Aikawa T, Aoshima C, Takamura K, Hiki M, Yokoyama T, Miyazaki T, Fujmoto S, Konishi H, Hirano KI, Daida H, Minamino T: Triglyceride deposit cardiomyovasculopathy with massive myocardial triglyceride which was proven using proton-magnetic resonance spectroscopy. Intern Med, 2021; 60: 1217–1220.

150) Werner GS, Lorenz S, Yaginuma K, Koch M, Tischer K, Werner J, Keuser T, Moehlis H, Riegel W: A prospective study on the incidence of contrast-associated acute kidney injury after recanalization of chronic total coronary occlusions with contemporary interventional techniques. Int J Cardiol, 2021; 337: 38–43.

151) Werner GS, Yaginuma K, Koch M, Tischer K, Silber K, Werner J, Keuser T, Moehlis H: Modulated radiation protocol achieves marked reduction of radiation exposure for chronic total occlusion intervention. Catheter Cardiovasc Interv, 2021; 97: 1196–1206

152) Yaginuma K, Werner GS: My experiences and challenges in German as a clinical physician –Acquire theory and skill of chronic total occlusion percutaneous coronary intervention and a German doctor's license–. Juntendo Medical Journal, 2021; 67: 119–123.

153) Werner GS, Yaginuma K, Koch M, Tischer K, Silber M, Werner J, Keuser T, Moehlis H: Reducing fluoroscopic and cineangiographic contribution to radiation exposure for chronic total coronary occlusion interventions. Cardiovasc Revasc Med, 2021; S1553–8389: 00208–6.

154) Werner GS, Yaginuma K: Left ventricular dysfunction in patients with a chronic total coronary occlusion and the benefit from revascularization. Cardiovasc Revasc Med, 2021; S1553–8389: 00152–4.

155) Kaneko T, Miyazaki S, Koike T, Murata A, Morimoto R, Hirose K, Takamura K, Endo D, Amano A, Minamino T: A Case of atypical Shone's complex diagnosed at 70 Years old: Presenting with double-orifice mitral valve, bicuspid aortic valve, and aortic coarctation. Intern Med, 2021. doi: 10.2169/internalmedicine.8176-21.

156) Shimizu M, Miyazaki T, Takagi A, Sugita Y, Ouchi S, Aikawa T, Shiozawa T, Hiki M, Takahashi S, Hiki M, Shimada K, Daida H: Low coenzyme Q10 levels in patients with acute cardiovascular disease are associated with long-term mortality. Heart Vessels, 2021; 36: 401–407.

157) Akita K, Isoda K, Ohtomo F, Isobe S, Niida T, Sato-Okabayashi Y, Sano M, Shimada K, Iwakura Y, Minamino T: Blocking of interleukin-1 suppresses angiotensin II-induced renal injury. Clin Sci (Lond), 2021; 135: 2035–2048.

158) Koga S, Ikeda S, Akashi R, Yonekura T, Kawano H, Maemura K: Serum soluble Klotho is inversely related to coronary artery calcification assessed by intravascular ultrasound in patients with stable coronary artery disease. J Cardiol, 2021; 77: 583–589.

159) Akashi R, Koga S, Yonekura T, Ikeda S, Kawano H, Maemura K: Cardio-ankle vascular index is associated with coronary plaque composition assessed with iMAP-intravascular ultrasound in patients with coronary artery disease. J Cardiol, 2021; 78: 502–508.

160) Chiba A, Kudo T, Ideguchi R, Altay M, Koga S,

Yonekura T, Tsuneto A, Morikawa M, Ikeda S, Kawano H, Koide Y, Uetani M, Maemura K: Usefulness of an artificial neural network for a beginner to achieve similar interpretations to an expert when examining myocardial perfusion images. Int J Cardiovasc Imaging, 2021; 37: 2337–2343.

161) Kanno T, Tatsuzawa M, Kinjo N, Kim S, Osanai M, Miyoshi T, Kojima Y, Sumiyoshi M, Shimo Y: Effect of Coadministration of atorvastatin and magnesium oxide on the rate of change in LDL cholesterol –A retrospective clinical study–. Jpn Pharmacol Ther, 2021; 49: 1001–1007.

162) Sumiyoshi M: A clinical study starting from an encounter with a patient. Juntendo Medical Journal, 2021; 67: 445–449.

163) Funamizu T, Nagatomo Y, Saji M, Iguchi N, Daida H, Yoshikawa T: Low muscle mass assessed by psoas muscle area is associated with clinical adverse events in elderly patients with heart failure. PLoS One, 2021; 16: e0247140.

164) Shiozaki M, Inoue K, Suwa S, Lee CC, Chiang SJ, Sato A, Shimizu M, Fukuda K, Hiki M, Kubota N, Tamura H, Fujiwara Y, Ouchi S, Miyazaki T, Hirano Y, Tanaka H, Sugita M, Nakazato Y, Sumiyoshi M, Daida H: Clinical evaluation of a new high-sensitivity cardiac troponin I assay for diagnosis and risk assessment of patients with suspected acute myocardial infarction. Cardiology, 2021; 146: 172–178. doi: 10.1159/000512185. Epub 2021 Jan 18.

165) Giannitsis E, Blankenberg S, Christenson RH, Frey N, von Haehling S, Hamm CW, Inoue K, Katus HA, Lee CC, McCord J, Möckel M, Chieh JTW, Tubaro M, Wollert KC, Huber K: Critical appraisal of the 2020 ESC guideline recommendations on diagnosis and risk assessment in patients with suspected non-ST-segment elevation acute coronary syndrome. Clin Res Cardiol, 2021; 110: 1353–1368.

166) Chiang CH, Chiang CH, Pickering JW, Stoyanov KM, Chew DP, Neumann JT, Ojeda F, Sörensen NA, Su KY, Kavsak P, Worster A, Inoue K, Johannessen TR, Atar D, Amann M, Hochholzer W, Mokhtari A, Ekelund U, Twerenbold R, Mueller C, Bahrmann P, Buttinger N, Dooley M, Ruangsomboon O, Nowak RM, DeFilippi CR, Peacock WF, Neilan TG, Liu MA, Hsu WT, Lee GH, Tang PU, Ma KS, Westermann D, Blankenberg S, Giannitsis E, Than MP, Lee CC: Performance of the European Society of Cardiology 0/1-Hour, 0/2-Hour, and 0/3-Hour Algorithms for Rapid Triage of Acute Myocardial Infarction : An International Collaborative Meta-analysis. Ann Intern Med, 2021.

167) Sunayama T, Yatsu S, Matsue Y, Dotare T, Maeda D, Ishiwata S, Nakamura Y, Suda S, Kato T, Hiki M, Kasai T, Minamino T: Urinary liver-type fatty acid-binding protein as a prognostic marker in patients with acute heart failure. ESC Heart Fail, 2021.

168) Ishiwata S, Kasai T, Sato A, Suda S, Matsumoto H, Shitara J, Yatsu S, Murata A, Shimizu M, Kato T, Hiki M, Matsue Y, Naito R, Daida H, Minamino T: Prognostic effect of sleep-disordered breathing on hospitalized patients following acute heart failure. Clin Res Cardiol, 2021.

169) Vulesevic B, Kubota N, Burwash IG, Cimadevilla C, Tubiana S, Duval X, Nguyen V, Arangalage D, Chan KL, Mulvihill EE, Beauchesne L, Messika-Zeitoun D: Size-adjusted aortic valve area: refining the definition of severe aortic stenosis. Eur Heart J Cardiovasc Imaging, 2021; 10: 1093.

170) Kunimoto K, Shimada K, Yokoyama M, Minamino T: Relationship between skin autofluorescence levels and clinical events in patients with heart failure undergoing cardiac rehabilitation. Cardiovascular Diabetology, 2021; 20: 208.

171) Hagiwara-Nagasawa M, Kambayashi R, Goto A, Nunoi Y, Izumi-Nakaseko H, Chiba K, Wada T, Takei Y, Matsumoto A, Sugiyama A*: Analysis of electropharmacological and proarrhythmic effects of donepezil using the halothane-anesthetized intact dogs and the conscious chronic atrioventricular block ones. Naunyn Schmiedebergs Arch Pharmacol, 2021; 394: 581–589.

172) Wada T, Hagiwara-Nagasawa M, Kambayashi R, Goto A, Chiba K, Nunoi Y, Izumi-Nakaseko H, Koga T, Matsumoto A, Nakazato Y, Lurie K, Sugiyama A*: Impact of cardiac massage and β-blocker pretreatment on the success rate of cardiopulmonary resuscitation assessed by the canine ischemia/reperfusion-induced ventricular fibrillation model. Circ J, 2021; 85: 1885–1891.

173) Hagiwara-Nagasawa M, Kambayashi R, Goto A, Chiba K, Wada T, Nunoi Y, Izumi-Nakaseko H, Takei Y, Matsumoto A, Lurie K, Sugiyama A*: Effects of mechanical ventilation with expiratory negative airway pressure on porcine pulmonary and systemic circulation: mechano-physiology and potential application. J Physiol Sci, 2021; 71: 17.

174) Yamagishi M, Tamaki N, Akasaka T, Ikeda T, Ueshima K, Uemura S, Otsuji Y, Kihara Y, Kimura K, Kimura T, Kusama Y, Kumita S, Sakuma H, Jinzaki M, Daida H, Takeishi Y, Tada H, Chikamori T, Tsujita K, Teraoka K, Nakajima K, Nakata T, Nakatani S, Nogami A, Node K, Nohara A, Hirayama A, Funabashi N, Miura M, Mochizuki T, Yokoi H, Yoshioka K, Watanabe M, Asanuma T, Ishikawa Y, Ohara T, Kaikita K, Kasai T, Kato E, Kamiyama H, Kawashiri M, Kiso K, Kitagawa K, Kido T, Kinoshita T, Kiriyama T, Kume T, Kurata A, Kurisu S, Kosuge M, Kodani E, Sato A, Shiono Y, Shiomi H, Taki J, Takeuchi M, Tanaka A, Tanaka N, Tanaka R, Nakahashi T, Nakahara T, Nomura A, Hashimoto A, Hayashi K, Higashi M, Hiro T, Fukamachi D, Matsuo H, Matsumoto N, Miyauchi K, Miyagawa M, Yamada Y, Yoshinaga K, Wada H, Watanabe T, Ozaki Y, Kohsaka S, Shimizu W, Yasuda S, Yoshino H; Japa-

nese Circulation Society Working Group: JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases. Circ J, 2021; 85: 402–572.

175) Fukaya H, Ako J, Yasuda S, Kaikita K, Akao M, Matoba T, Nakamra M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H: Aspirin versus P2Y12 inhibitors with anticoagulation therapy for atrial fibrillation. Heart, 2021; 107: 1731–1738.

176) Kato Y, Dohi T, Chikata Y, Fukase T, Takeuchi M, Takahashi N, Endo H, Nishiyama H, Doi S, Okai I, Iwata H, Isoda K, Okazaki S, Miyauchi K, Daida H, Minamino T: Predictors of discordance between fractional flow reserve and resting full-cycle ratio in patients with coronary artery disease: Evidence from clinical practice. J Cardiol, 2021; 77: 313–319.

177) Ueda R, Nishizaki Y, Nojiri S, Iwata H, Miyauchi K, Matsuyama K, Sanada S, Minamino T, Daida H: Factors Associated With the Acceleration of Patient Enrollment in Clinical Studies: A Cross-Sectional Study. Front Pharmacol, 2021; 12: 753067.

178) Matoba T, Yasuda S, Kaikita K, Akao M, Ako J, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators: Rivaroxaban Monotherapy in Patients With Atrial Fibrillation After Coronary Stenting: Insights From the AFIRE Trial. JACC Cardiovasc Interv, 2021; 14: 2330–2340.

179) Emoto R, Yatsu S, Yoshihara T, Sai E, Miyazaki T, Yamamoto T, Amano A, Daida H, Miyauchi K: Successful Surgical and Endovascular Multidisciplinary Therapy for Mid-aortic Syndrome with Complicated Atherosclerotic Comorbidities in an Older Patient. Intern Med, 2021.

180) Yazaki Y, Nakamura M, Iijima R, Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators: Clinical Outcomes of Rivaroxaban Monotherapy in Heart Failure Patients With Atrial Fibrillation and Stable Coronary Disease: Insights From the AFIRE Trial. Circulation, 2021; 144: 1449–1451.

181) Fukase T, Dohi T, Koike T, Yasuda H, Takeuchi M, Takahashi N, Chikata Y, Endo H, Doi S, Nishiyama H, Okai I, Iwata H, Okazaki S, Miyauchi K, Daida H, Minamino T: Long-term impact of β-blocker in elderly patients without myocardial infarction after percutaneous coronary intervention. ESC Heart Fail, 2021.

182) Ishii J, Kashiwabara K, Ozaki Y, Takahashi H, Kitagawa F, Nishimura H, Ishii H, Iimuro S, Kawai H, Muramatsu T, Naruse H, Iwata H, Tanizawa-Motoyama S, Ito H, Watanabe E, Matsuyama Y, Fukumoto Y, Sakuma I, Nakagawa Y, Hibi K, Hiro T, Hokimoto S, Miyauchi K, Ohtsu H, Izawa H, Ogawa H, Daida H, Shimokawa H, Saito Y, Kimura T, Matsuzaki M, Nagai R: Small Dense Low-Density Lipoprotein Cholesterol and Cardiovascular Risk in Statin-Treated Patients with Coronary Artery Disease. J Atheroscler Thromb, 2021.

183) Takeuchi M, Dohi T, Takahashi N, Endo H, Doi S, Kato Y, Okai I, Iwata H, Okazaki S, Isoda K, Miyauchi K, Minamino T: The prognostic implications of chronic kidney disease and anemia on long-term outcomes in patients undergoing percutaneous coronary intervention. Heart Vessels, 2021; 36: 1117–1124.

184) Nishio R, Dohi T, Takeuchi M, Takahashi N, Endo H, Doi S, Okai I, Iwata H, Okazaki S, Miyauchi K, Daida H, Minamino T: Combined impact of residual inflammatory risk and chronic kidney disease on long-term clinical outcomes in patients undergoing percutaneous coronary intervention. J Cardiol, 2021: S0914-5087: 00301-4.

185) Abe M, Ozaki Y, Takahashi H, Ishii M, Masunaga N, Ismail TF, Iimuro S, Fujita R, Iwata H, Sakuma I, Nakagawa Y, Hibi K, Hiro T, Fukumoto Y, Hokimoto S, Miyauchi K, Ogawa H, Daida H, Shimokawa H, Saito Y, Matsuzaki M, Akao M, Kimura T, Nagai R: Relation of renal function to mid-term prognosis of stable angina patients with high- or low-dose pitavastatin treatment: REAL-CAD substudy. Am Heart J, 2021; 240: 89–100.

186) Matsuzawa Y, Kimura K, Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators: Antithrombotic Therapy for Atrial Fibrillation and Coronary Artery Disease in Patients With Prior Atherothrombotic Disease: A Post Hoc Analysis of the AFIRE Trial. J Am Heart Assoc, 2021; 10: e020907.

187) Kaikita K, Yasuda S, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H: Bleeding and Subsequent Cardiovascular Events and Death in Atrial Fibrillation With Stable Coronary Artery Disease: Insights From the AFIRE Trial. Circ Cardiovasc Interv, 2021; 14: e010476.

188) Noguchi M, Dohi T, Okazaki S, Matsumura M, Takeuchi M, Endo H, Kato Y, Okai I, Nishiyama H, Doi S, Iwata H, Isoda K, Usui E, Fujimura T, Seike F, Mintz GS, Miyauchi K, Daida H, Minamino T, Maehara A: Comparison of 6-month vascular healing response after bioresorbable polymer versus durable polymer drug-eluting stent implantation in patients with acute coronary syndromes: A randomized serial optical coherence tomography study. Catheter Cardiovasc Interv, 2021; 98: E677–E686.

189) Akao M, Yasuda S, Kaikita K, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H: Rivaroxaban monotherapy versus combination therapy according to patient risk of stroke and bleeding in atrial fibrillation and stable coronary disease: AFIRE trial subanalysis. Am Heart J, 2021; 236: 59–68.

190) Shimizu M, Miyazaki T, Takagi A, Sugita Y, Ouchi S, Aikawa T, Shiozawa T, Hiki M, Takahashi S, Hiki M, Shimada K, Daida H: Low coenzyme Q10 levels in patients with acute cardiovascular disease are associated with long-term mortality. Heart Vessels, 2021; 36: 401-407.
191) Nishitani-Yokoyama M, Shimada K, Yamada M, Honzawa A, Kunimoto M, Sugita Y, Fujiwara K, Matsubara T, Matsumori R, Abulimiti A, Shimada A, Yamamoto T, Asai T, Amano A, Saitoh M, Morisawa T, Takahashi T, Daida H, Minamino T: Association Between Constipation and Frailty Components in Patients Undergoing Late Phase II Cardiac Rehabilitation. Cardiol Res, 2021; 12: 169-176.
192) Abulimiti A, Nishitani-Yokoyama M, Shimada K, Kunimoto M, Matsubara T, Fujiwara K, Aikawa T, Ouchi S, Sugita Y, Fukao K, Kadoguchi T, Miyazaki T, Shimada A, Yamamoto T, Takahashi T, Fujiwara T, Asai T, Amano A, Daida H, Minamino T: Prognostic impact of peak oxygen uptake and heart rate reserve in patients after off-pump coronary artery bypass grafting. Clin Cardiol, 2021; 44: 580-587.
193) Wada H, Ogita M*, Suwa S, Nakao K, Ozaki Y, Kimura K, Ako J, Noguchi T, Yasuda S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Saito Y, Hirohata A, Morita Y, Inoue T, Okamura A, Mano T, Hirata K, Tanabe K, Shibata Y, Owa M, Tsujita K, Funayama H, Kokubu N, Kozuma K, Uemura S, Toubaru T, Saku K, Oshima S, Nishimura K, Miyamoto Y, Ogawa H, Ishihara M; J-MINUET investigators: Prediction of long-term outcomes in ST-elevation myocardial infarction and non-ST segment myocardial infarction with and without creatinine kinase elevation-post-hoc analysis of the J-MINUET study. Int Heart J, 2021; 62: 520-527.
194) Kimura T, Akahori H*, Asakura M, Nakao K, Ozaki Y, Kimura K, Ako J, Noguchi T, Suwa S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Saito Y, Hirohata A, Morita Y, Inoue T, Okamura A, Mano T, Wake M, Tanabe K, Shibata Y, Owa M, Tsujita K, Funayama H, Kokubu N, Kozuma K, Uemura S, Toubaru T, Saku K, Oshima S, Nishimura K, Miyamoto Y, Ogawa H, Ishihara M; J-MINUET investigators: Impact of age on gender difference in long-term outcome of patients with acute myocardial infarction (from J-MINUET. Am J Cardiol, 2021; 142: 5-13.
195) Matumura-Nakano Y, Shiomi H, Morimoto T, Yamaji K, Ehara N, Sakamoto H, Takeji Y, Yoshikawa Y, Yamamoto K, Imada K, Tada T, Taniguchi R, Nishikawa R, Tada T, Uegaito T, Ogawa T, Yamada M, Takeda T, Eizawa H, Tamura N, Tambara K, Suwa S, Shirotani M, Tamura T, Inoko M, Nishizawa J, Natuaki M, Sakai H, Yamamoto T, Kanemitsu N, Ohno N, Ishii K, Marui A, Tsuneyoshi H, Terai Y, Nakayama S, Yamazaki K, Takahashi M, Tamura T, Esaki J, Miki S, Onodera T, Mabuchi H, Furukawa Y, Tanaka M, Komiya T, Soga Y, Hanyu M, Ando K, Kadota K, Minatoya K, Nakagawa Y, Kimura T*; CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators: Comparison of outcomes of percutaneous coronary intervention versus coronary artery bypass grafting among patients with three-vessel coronary artery disease in the new generation drug-eluting stents era (from the CREDO-Kyoto PCI/CABG Registry Cohort-3). Am J Cardiol, 2021; 145: 25-36.
196) Yamamoto K, Shiomi H*, Morimoto T, Kadota K, Tada T, Takeji Y, Matsumura-Nakano Y, Yoshikawa Y, Imada K, Domei T, Kaneda K, Taniguchi R, Ehara N, Nawada R, Natsuaki M, Yamaji K, Toyofuku M, Kanemitsu N, Shinoda E, Suwa S, Iwakura A, Tamura T, Soga Y, Inada T, Matsuda M, Koyama T, Aoyama T, Sato Y, Furukawa Y, Ando K, Yamazaki F, Komiya T, Minatoya K, Nakagawa Y, Kimura T; CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators: Percutaneous coronary intervention versus coronary artery bypass grafting among patients with unprotected left main coronary artery disease in the new-generation drug-eluting stents era (from the CREDO-Kyoto Registry Cohort-3). Am J Cardiol, 2021; 145: 47-57.
197) Yamamoto K, Natsuaki M, Morimoto T, Shiomi H, Takeji Y, Kadota K, Imada K, Toyofuku M, Kanemitsu N, Shinoda E, Suwa S, Iwakura A, Tamura T, Soga Y, Inada T, Matsuda M, Koyama T, Aoyama T, Kato E, Sato Y, Furukawa Y, Ando K, Yamazaki F, Komiya T, Minatoya K, Nakagawa Y, Kimura T*; CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators: Percutaneous coronary intervention versus coronary artery bypass grafting in patients with versus without chronic kidney disease. Am J Cardiol, 2021; 145: 37-46.
198) Watanabe H, Morimoto T, Ogita M, Suwa S, Natsuaki M, Suematsu N, Koeda Y, Morino Y, Nikaido A, Hata Y, doi M, Hibi K, Kimura K, Yoda S, Kaneko T, Nishida K, Kazai K, Yamaguchi K, Wakatsuki T, Tonoike N, Yamamoto M, Shimizu S, Shimohama T, Ako J, Kimura T*, on behalf of STOPDAPT-2 investigators: Influence of CYP2C19 genotypes for the effect of 1-month dual antiplatelet therapy followed by clopidogrel monotherapy relative to 12-month dual antiplatelet therapy on clinical outcomes after percutaneous coronary intervention; A genetic substudy from the STOPDAPT-2. Cardiovasc Interv Ther, 2021; 36: 403-415.
199) Shiozaki M, Inoue K*, Suwa S, Lee CC, Chiang SJ, Sato A, Fukuda K, Kubota N, Tamura H, Fujiwara Y, Yamaguchi K, Sato T, Sumiyoshi M, Daida H: Clinical evaluation of a new high-sensitivity cardiac troponin I assay for diagnosis and risk assessment of patients with suspected acute myocardial infarction. Cardiology, 2021; 146: 172-178.
200) Soeda T, Okura H, Saito Y, Nakao K, Ozaki Y, Kimura

K, Ako J, Noguchi T, Yasuda S, Suwa S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Hirohata A, Morita Y, Inoue T, Okamura A, Mano T, Hirata K, Tanabe K, Shibata Y, Owa M, Tsujita K, Funayama H, Kokubu N, Kozuma K, Uemura S, Toubaru T, Saku K, Oshima S, Nishimura K, Miyamoto Y, Ogawa H, Ishihara M; J-MINUET investigators: Clinical characteristics and in-hospital outcomes in patients aged 80 years or over with cardiac troponin-positive acute myocardial infaction-J-MINUET study. J Cardiol, 2021; 77: 139-146.

201) Takeji Y, Shiomi H*, Morimoto T, Yoshikawa Y, Taniguchi R, Matsumura-Nakano Y, Yamamoto K, Yamaji K, Tazaki J, Suwa S, Inoko M, Takeda Y, Shirotani M, Ehara N, Ishii K, Inada T, Onodera T, Shinoda E, Yamamoto T, Tamura T, Nakatsuma K, Sakamoto H, Ando K, Soga Y, Furukawa Y, Sato Y, Nakagawa Y, Kadota K, Komiya T, Minatoya K, Kimura T. CREDO-Kyoto PCI/CABG Registry Cohort-2 and CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators: Demographics and practice patterns and long-term outcomes of patients with non-ST-segment elevation acute coronary syndrome in the past two decades: the CREDO-Kyoto Cohort-2 and Cohort-3. BMJ Open, 2021; 11: e044329.

202) Yamamoto K, Watanabe H, Morimoto T, Domei T, Ohya M, Ogita M, Takagi K, Suzuki H, Nikaido A, Ishii M, Fujii S, Natsuaki M, Yasuda S, Kaneko T, Tamura T, Tamura T, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Igarashi Hanaoka K, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T*. On behalf of the STOPDAPT-2 investigatotrs: Very short dual antiplatlet therapy after drug-eluting stent implantation in patients who underwent complex percutantous coronary intervention: Insight from the STOPDAPT-2 Trial. Circ Cardiovasc Interv, 2021; 14: e010384.

203) Matoba T, Sakamoto K, Nakai M, Ichimura K, Mohri M, Tsujita Y, Yamasaki M, Ueki Y, Tanaka N, Hokama Y, Fukutomi M, Hashiba K, Fukuhara R, Suwa S, Matsuura H, Hosoda H, Nakashima T, Tahara Y, Sumita Y, Nishimura K, Miyamoto Y, Yonemoto N, Yagi T, Tachibana E, Nagao K, Ikeda T, Sato N, Tsutsui H: Institutional characteristics and prognosis of acute myocardial infarction with cardiogenic shock in Japan - Analysis from the JROAD/JROAD-DPC database. Circ J, 2021; 85: 1797-1805.

204) Natsuaki M*, Morimoto T, Shiomi H, Kadota K, Tada T, Takeji Y, Matsumura-Nakano Y, Yoshikawa Y, Watanabe H, Yamamoto K, Imada K, Domei T, Yamaji K, Tazaki J, Kaneda K, Taniguchi R, Ehara N, Nawada R, Toyofuku M, Shinoda E, Suwa S, Tamura T, Inada T, Matsuda M, Aoyama T, Sato Y, Furukawa Y, Ando K, Nakagawa Y, Kimura T: CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators. Effect of acute coronary syndrome and stable coronary artery disease on bleeding and ischemic risk after percutaneous coronary intervention. Circ J, 2021. doi: 10.1253. (Online ahead of print).

205) Naruse Y, Miyajima K, Sugiura R, Muto M, Ogano M, Kurebayashi N, Shiozawa T, Kiyama Y, Nagata E, Odagiri K, Maekawa Y; Mt. FUJI trial investigators: Comparison of delivery catheter-based and stylet-based right ventricular lead placement at the right ventricular septum under fluoroscopic guidance judged by cardiac CT (Mt. FUJI): a study protocol for the Mt. FUJI randomized controlled trial. BMJ Open, 2021; 11: e046782.

206) Natsuaki M, Morimoto T, Shiomi H, Ehara N, Taniguchi R, Tamura T, Tada T, Suwa S, Kaneda K, Watanabe H, Tazaki J, Wanatabe S, Yamamoto E, Saito N, Fuki M, Takeda T, Eizawa H, SInoda E, Mabuchi H, Shirotani M, Uegaito T, Matsuda M, Takahashi M, Inoko M, Tamura T, Ishii K, Onodera T, Sakamoto H, Aoyama T, Sato Y, Ando K, Furukawa Y, Nakagawa Y, Kadota, K, Kimura T*: Application of the modified high bleeding risk criteria for Japanese patients in an all-comers registry of percutaneous coronary intervention -From the CREDO-Kyoto Registry Cohort -3. Cir J, 2021; 85: 769-781.

207) Hashimoto Y, Ozaki Y*, Kan S, Nakao K, Kimura K, Ako J, Noguchi T, Suwa S, Fujimoto K, Dai K, Morita T, Shimizu W, Saito Y, Hirohata A, Morita Y, Inoue T, Okamura A, Mano T, Wake M, Tanabe K, Shibata Y, Owa M, Tsujita K, Funayama H, Kokubu N, Kozuma K, Uemura S, Tobaru T, Saku K, Oshima S, Yasuda S, Ismail TF, Muramatsu T, Izawa H, Takahashi H, Nishimura K, Miyamoto Y, Ogawa H, Ishihara M; J-MINUET investigators: Impact of chronic kidney disease on in-hospital and 3-year clinical outcomes in patients with acute myocardial infarction treated by contemporary percutaneous coronary intervention and optima medical therapy - Insights from the J-MINUET study. Circ J, 2021; 85: 1710-1718.

208) Shiomi H*, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Yoshikawa Y, Yamaji K, Tada T, Tazaki J, Ehara N, Taniguchi R, Tamura T, Iwakura A, Tada T, Watanabe H, Suwa S, Toyofuku M, Inada T, Kaneda K, Ogawa T, Takeda T, Sakai H, Yamamoto T, Tambara K, Esaki J, Eizawa H, Yamada M, Shinoda E, Nishizawa J, Mabuchi H, Tamura N, Shirotani M, Nakayama S, Uegaito T, Matsuda M, Takahashi M, Inoko M, Kanemitsu N, Tamura T, Ishii K, Nawada R, Onodeara T, Ohno N, Koyama T, Tsuneyohsi H, Sakamoto H, Aoyoama T, Miki S, Tanaka M, Sato Y, Yamazaki F, Hanyu M, Soga Y, Komiya T, Ando K, Minatoya K, Kimura T. CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators: Coronary revascularization in the past two decades in Japan (from the CREDO-Kyoto PCI/CABG Registry Cohort-1, -2, and -3). Am J Cardiol, 2021; 153: 20-29.

209) Yamamoto K, Matsumura-Nakano Y, Shiomi H,

Natsuaki M, Morimoto T, Kadota K, Tada T, Takeji Y, Yoshikawa Y, Imada K, Domei T, Kaneda K, Taniguchi R, Ehara N, Nawada R, Yamaji K, Kato E, Toyofuku M, Kanemitsu N, Shinoda E, Suwa S, Iwakura A, Tamura T, Soga Y, Inada T, Matsuda M, Koyama T, Aoyama T, Sato Y, Furukawa Y, Ando K, Yamazaki F, Komiya T, Minatoya K, Nakagawa Y, Kimura T*; CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators: Effect of heart failure on long-term clinical outcomes after percutaneous coronary intervention versus coronary artery bypass grafting in patients with severe coronary artery disease. J Am Heart Assoc, 2021; 10: e021257.

210) Asakura M, Hibi K, Shimizu W, Fujii K, Suwa S, Okumura Y, Mano T, Igeta M, Okamoto R, Ishihara M: Design and rationale of the EVOCATION trial: A prospective, randomized, exploratory study comparing the effect of evolocumab on coronary microvascular function after percutaneous coronary intervention in patients with stable coronary artery disease. J Cardiol, 2021; S0914-5087: 00228-8.

211) Natsuaki M, Morimoto T, Shiomi H, Yamamoto K, Yamaji K, Watanabe H, Uegaito T, Matsuda M, Tamura T, Taniguchi R, Inoko M, Mabuchi H, Takeda T, Domei T, Shirotani M, Ehara N, Eizawa H, Ishii K, Tanaka M, Inada T, Onodera T, Nawada R, Shinoda E, Yamada M, Yamanoto T, Sakai H, Toyofuku M, Tamura T, Takahashi M, Tada T, Sakamoto H, Tada T, Kaneda K, Miki S, Aoyama T, Suwa S, Sato Y, Ando K, Furukawa Y, Nakagawa Y, Kadota, K, Kimura T*: Bleeding outcomes after percutaneous coronary intervention in the past two decades in Japan – From the CREDO-Kyoto Registry Cohort -2 and Cohort -3. Cir J, 2021. (Online ahead of print).

212) Obayashi Y, Shiomi H*, Morimoto T, Tamai Y, Inoko M, Yamamoto K, Takeji Y, Tada T, Nagao K, Yamaji K, Kaneda K, Suwa S, Tamura T, Sakamoto H, Inada T, Matsuda M, Sato Y, Furukawa Y, Ando K, Kadota K, Nakagawa Y, Kimura K; CREDO-Kyoto AMI Registry Wave-2 Investigators: Newly diagnosed atrial fibrillation in acute myocardial infarction. J Am Heart Assoc, 2021; 10: e021417.

213) Hashimoto T, Minami Y, Ako J*, Nakao K, Ozaki Y, Kimura K, Noguchi T, Suwa S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Saito Y, Hirohata A, Morita Y, Inoue T, Okamura A, Mano T, Hirata K, Tanabe K, Shibata Y, Owa M, Tsujita K, Funayama H, Kokubu N, Kozuma K, Uemura S, Tobaru T, Saku K, Oshima S, Nishimura K, Miyamoto Y, Ogawa H, Ishihara M; J-MINUET investigators: Validation of the atherothrombotic risk score for secondary prevention in patients with acute myocardial infarction: the J-MINUET study. Heart Vessels, 2021; 36: 1506-1513.

214) Takeji Y, Shiomi H, Morimoto T, Yamamoto K, Matsumura-Nakano Y, Nagao K, Taniguchi R, Yamaji K, Tada T, Toda-Kato E, Yoshikawa Y, Obayashi Y, Suwa S, Inoko M, Ehara N, Tamura T, Onodera T, Watanabe H, Toyofuku M, Nakatsuma K, Sakamoto H, Ando K, Furukawa Y, Sato Y, Nakagawa Y, Kadota, K, Kimura T, CREDO-Kyoto AMI Registry Wave-2 Investigators: PLoS One. 2021; 16: e0259268.

215) Ishiwata S, Kasai T, Sato A, Suda S, Matsumoto H, Shitara J, Yatsu S, Murata A, Shimizu M, Murata A, Kato T, Hiki M, Matsue Y, Naito R, Daida H, Minamino T: Prognostic effects of arterial carbon dioxide levels in patients hospitalized into the cardiac intensice care unit for acute heart failure. Eur Heart J Acute Cardiovasc Care, 2021; 10: 497-502.

216) Murasato Y, Yamaji K, Kohsaka S, Wada H, Ishii H, Kinoshita Y, Shite J, Hikichi Y, Amano T, Ikari Y: Percunateous coronary interventioni in side branch coronary arteries: Insights from the Japanese nationwide registry. Int J Cardiol Heart Vasc, 2021; 36: 100856.

217) Ito T, Yamaji K, Kohsaka S, Ishii H, Wada H, Amano T, Fujita H, Seo Y, Ikari Y: Effect of Procedural Volume on In-Hospital Outcomes After Percutaneous Coronary Intervention in Patients With Chronic Kidney Disease (from the Japanese National Clinical Data [J-PCI Registry]) Am J Cardiol, 2021; S0002-9149: 01098-5.

〈Reviews〉

1) Tanaka S, Yamashita M, Siato H, Kamiya K, Maeda D, Konishi M, Matsue Y*: Multidomain Frailty in Heart Failure: Current Status and Future Perspectives. Curr Heart Fail Rep, 2021; 18: 107-120.

2) Sunayama T, Matsue Y*, Dotare T, Maeda D, Iso T, Morisawa T, Saitoh M, Yokoyama M, Jujo K, Takahashi T, Minamino T: Miltidomain frailty as a therapertic target in old patients with heart failure. Int Heart J, 2021; in-press.

3) Matsuzawa Y, Kimura K, Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators: Antithrombotic Therapy for Atrial Fibrillation and Coronary Artery Disease in Patients With Prior Atherothrombotic Disease: A Post Hoc Analysis of the AFIRE Trial. J Am Heart Assoc, 2021; 10: e020907.

〈Books〉

1) Katsuumi G, Minamino T: Cellular Senescence in Disease. 1st Edition – November 27, 2021. Editors: Manuel Serrano, Daniel Munoz-Espin. eBook ISBN: 9780128225158. Paperback ISBN: 9780128225141. Chapter 9. Vascular diseases. ii. Atherosclerosis and atherosclerotic cardiovascular diseases.

2) Kagiyama N, Shrestha S, Sengupta PP: "Future Applications of Strain Imaging". ASE's Comprehensive Strain Imaging. Elsevier, 2021; 220-223.

3) Katsuumi G, Minamino T: chapter 9: Vascular diseases:atherosclerosis and Atherosclerotic cardiovascular diseases. Serrano M & Muñoz-Espín DCellular.

Senescence in Disease – 1st edition, 2021; 227–268.

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〈Original Articles〉

1) Ueyama H, Murakami T, Matsumoto K, Sakamoto N, Osada T, Yao T, Nagahara A: Modified attachment method using S-O clip and multibending scope for gastric ESD at the greater curvature of the fundus. Endosc Int Open.PMID: 33532558 PMCID: PMC7834921 DOI: 10.1055/a-1315-0293. Epub 2021 Jan 25. 2021; 9: E195–E196.
2) Matsumoto K, Sakamoto N, Murakami T, Yatagai N, Tsuyama S, Fukushima H, Ueyama H, Shibuya T, Yao T, Nagahara A: Long-term relapse-free treatment with endoscopic submucosal dissection combined with magnifying narrow-band imaging for a pregnant patient with flat-type condyloma acuminatum: a case report. Clin J Gastroenterol. 2021. PMID: 33394332 DOI: 10.1007/s12328-020-01288-0.
3) Yatagai N, Ueyama H, Ikemura M, Uchida R, Utsunomiya H, Abe D, Oki S, Suzuki N, Ikeda A, Akazawa Y, Komori H, Takeda T, Matsumoto K, Ueda K, Matsumoto K, Asaoka D, Hojo M, Tsuyama S, Hayashi T, Yao T, Nagahara A: Clinicopathological and Endoscopic Features of Raspberry-Shaped Gastric Cancer in Helicobacter pylori-Uninfected Patients. Digestion, 2021; 102: 41–48. PMID: 33321493 DOI: 10.1159/000511907
4) Shiroma S, Hatta W, Tsuji Y, Yoshio T, Yabuuchi Y, Hoteya S, Tsuji S, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Yamaguchi S, Michida T, Yada T, Asahina Y, Narasaka T, Kuribayashi S, Kiyotoki S, Mabe K, Fujishiro M, Masamune A, Fujisaki J: Timing of bleeding and thromboembolism associated with endoscopic submucosal dissection for gastric cancer in Japan. J Gastroenterol Hepatol, First published: 2021. Online ahead of print, PMID: 33960518,doi.org/10.1111/jgh.15536.
5) Hashimoto M, Hatta W, Tsuji Y, Yoshio T, Yabuuchi Y, Hoteya S, Doyama H, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Fujishiro M, Masamune A, Ohira H: Rebleeding in patients with delayed bleeding after endoscopic submucosal dissection for early gastric cancer. Dig Endosc,First published: 2021, Online ahead of print, PMID: 33539035,doi: 10.1111/den.13943.
6) Hojo M, Ueda K, Takeda T, Akazawa Y, Ueyama H, Shimada Y, Asaoka D, Nagahara A: The relationship between *Helicobacter pylori infection* and reflux esophagitis and the long-term effects of eradication of *Helicobacter pylori* on reflux esophagitis. Therap Adv Gastroenterol, 2021; 14: 17562848211059942.
7) Hojo M, Nagahara A, Kudo T, Takeda T, Ikuse T, Matsumoto K, Ueda K, Ueyama H, Matsumoto K, Asaoka D, Shimizu T: Endoscopic findings of *Helicobacter pylori* gastritis in children and young adults based on the Kyoto classification of gastritis and age-associated changes. JGH Open, 2021; 5: 1197–1202.
8) Kirita K, Kodaka Y, Shibata Y, Ueki N, Agawa S, Yamawaki H, Niikura R, Yamamichi N, Izumi K, Hojo M, Maruyama K, Yamamoto T, Gudis K, Watanabe M, Kaise M, Iwakiri K, Futagami S: Impact of clinical characteristics of colonic diverticular bleeding in extremely elderly patients treated with direct oral anti-coagulant drugs: a retrospective multi-center study. J Clin Biochem Nutr, 2021; 69: 222–228.
9) Ueyama H, Yao T, Akazawa Y, Hayashi T, Kurahara K, Oshiro Y, Yamada M, Oda I, Fujioka S, Kusumoto C, Fukuda M, Uchita K, Kadota T, Oono Y, Okamoto K, Murakami K, Matsuo Y, Kato M, Maehata T, Yahagi N, Yasuhara Y, Yada T, Uraushihara K, Yamane T, Matsuo T, Ito M, Maruyama Y, Osako A, Ono S, Kato M, Yagi K, Hashimoto T, Tomita N, Tsuyama S, Saito T, Matsumoto K, Matsumoto K, Watanabe S, Uemura N, Chiba T, Nagahara A: Gastric epithelial neoplasm of fundic-gland mucosa lineage: proposal for a new classification in association with gastric adenocarcinoma of fundic-gland type. J Gastroenterol, 2021; 56: 814–828, accepted: 10 July 2021. http://doi.org/10.1007/s0053-021-01813-z.
10) Ueyama H, Yatagai N, Ikeda A, Akazawa Y, Komori H, Takeda T, Matsumoto K, Ueda K, Matsumoto K, Asaoka D, Hojo M, Yao T, Nagahara A: Dynamic diagnosis of early gastric cancer with microvascular blood flow rate using magnifying endoscopy (with video): A pilot study. J Gastroenterol Hepatol, 2021; 36: 1927–1934.
11) Ueyama H, Kato Y, Akazawa Y, Yatagai N, Komori H, Takeda T, Matsumoto K, Ueda K, Matsumoto K, Hojo M, Yao T, Nagahara A, Tada T: Application of artificial intelligence using a convolutional neural network for diagnosis of early gastric cancer based on magnifying endoscopy with narrow-band imaging. J Gastroenterol Hepatol, 2021; 36: 482–489.
12) Hashimoto M, Hatta W, Tsuji Y, Yoshio T, Yabuuchi Y, Hoteya S, Doyama H, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Fujishiro M, Masamune A, Ohira H: Rebleeding in patients with delayed bleeding after endoscopic submucosal dissection for early gastric cancer. Dig Endosc, 2021; 33: 1120–1130.
13) Nagami Y, Hatta W, Tsuji Y, Yoshio T, Kakushima N, Hoteya S, Tsuji S, Fukunaga S, Hikichi T, Kobayashi

M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Yoshida H, Fujishiro M, Masamune A, Fujiwara Y: Antithrombotics increase bleeding after endoscopic submucosal dissection for gastric cancer: Nationwide propensity score analysis. Dig Endosc, 2021. doi: 10.1111/den.14151. Epub ahead of print. PMID: 34564863.

14) Shiroma S, Hatta W, Tsuji Y, Yoshio T, Yabuuchi Y, Hoteya S, Tsuji S, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Yamaguchi S, Michida T, Yada T, Asahina Y, Narasaka T, Kuribayashi S, Kiyotoki S, Mabe K, Fujishiro M, Masamune A, Fujisaki J: Timing of bleeding and thromboembolism associated with endoscopic submucosal dissection for gastric cancer in Japan: J Gastroenterol Hepatol, 2021; 36: 2769–2777.

15) Yabuuchi Y, Hatta W, Tsuji Y, Yoshio T, Kakushima N, Hoteya S, Doyama H, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Yamaguchi S, Michida T, Yada T, Asahina Y, Narasaka T, Kuribayashi S, Kiyotoki S, Mabe K, Fujishiro M, Masamune A, Ono H: Influence of hospital volume on bleeding after endoscopic submucosal dissection for early gastric cancer in Japan: a multicenter propensity score–matched analysis. Surg Endosc, 2021. doi: 10.1007/s00464–021–08721–6. Epub ahead of print. PMID: 34494147.

16) Murakami T, Sakamoto N, Fukushima H, Shibuya T, Yao T, Nagahara A: Usefulness of the Japan narrow–band imaging expert team classification system for the diagnosis of sessile serrated lesion with dysplasia/carcinoma. Surg Endosc, 2021; 35: 4528–4538.

17) Takasaki Y, Ishii S, Shibuya T, Fujisawa T, Ushio M, Takahashi S, Ito K, Yamagata W, Suzuki A, Okahara K, Okawa Y, Ochiai K, Tomishima K, Nomura O, Haga K, Saito H, Nagahara A, Isayama H: Endoscopic ultrasound–guided antegrade procedures for managing bile duct stones in patients with surgically altered anatomy: Comparison with double–balloon enteroscopy–assisted endoscopic retrograde cholangiography (with video). Dig Endosc, 2021; 33: 1179–1187.

＊ 18) Nomura K, Ishikawa D, Okahara K, Ito S, Haga K, Takahashi M, Arakawa A, Shibuya T, Osada T, Kuwahara–Arai K, Kirikae T, Nagahara A: Bacteroidetes Species Are Correlated with Disease Activity in Ulcerative Colitis. J Clin Med, 2021; 10: 1749.

19) Haraikawa M, Kudo H, Shibuya T, Kogure Y, Takase M, Inage H, Yokota T, Htun H, Tagaya E, Fan R, Houshito H, Taniguchi G, Sakamoto K, Nagahara A: Efficacy of CO_2 Infusion for Preoperative Computed Tomographic Angiography with Computed Tomographic Colonography. Med Sci Monit, 2021; 27: e931055.

20) Tomishima K, Ishii S, Fujisawa T, Ikemura M, Ushio M, Takahashi S, Yamagata W, Takasaki Y, Suzuki A, Ito K, Haga K, Ochiai K, Nomura O, Saito H, Shibuya T, Nagahara A, Isayama H: Evaluation of the Feasibility and Effectiveness of Placement of Fully Covered Self–Expandable Metallic Stents via Various Insertion Routes for Benign Biliary Strictures. J Clin Med, 2021; 10: 2397.

21) Shibuya T, Nomura O, Nagahara A: Safety and Efficacy of Ustekinumab for Ulcerative Colitis in a Liver Transplant Patient. Inflamm Bowel Dis, 2021.

22) Fujisawa T, Isayama H, Shibuya T, Tomishima K, Ishii S: Cholangioscopy and double–balloon enteroscopy mediated “sandwich puncture” of a completely closed choledochojejunostomy. VideoGIE, 2021; 6: 325–328.

23) Fukushima H, Sakamoto N, Shibuya T, Haga K, Nomura O, Murakami T, Ueyama H, Ishikawa D, Hojo M, Nagahara A: A Comparative Study of Early Mucosal Healing Following Hot Polypectomy and Cold Polypectomy. Med Sci Monit, 2021; 27: e933043.

24) Haga K, Shibuya T, Nomura K, Haraikawa M, Nomura O, Nagahara A: Jejunostomy tube removed after pancreaticoduodenectomy using single–balloon endoscopy. Endoscopy, 2021.

25) Maruyama T, Murakami T, Akazawa Y, Shibuya T, Nagahara A: A case of improved visibility with gel immersion in the presence of ongoing bleeding during colorectal endoscopic submucosal dissection. VideoGIE, 2021; 6: 478–480.

26) Nakajima A, Shibuya T, Sasaki T, Lu YJ, Ishikawa D, Haga K, Takahashi M, Kaga N, Osada T, Sato N, Nagahara A: Nicotine Oral Administration Attenuates DSS–Induced Colitis Through Upregulation of Indole in the Distal Colon and Rectum in Mice. Front Med (Lausanne), 2021; 8: 789037.

27) Kanesaka T, Uedo N, Doyama H, Yoshida N, Nagahama T, Ohtsu K, Uchita K, Kojima K, Ueo T, Takahashi H, Ueyama H, Akazawa Y, Shimokawa T, Yao K: Diagnosis of histological type of early gastric cancer by magnifying narrow–band imaging: A multicenter prospective study. Den Open.Volume2, Issue1 April 2022 e61First published: 28 September 2021 https://doi.org/10.1002/deo2.61.

28) Kato M, Takeuchi Y, Hoteya S, Oyama T, Nonaka S, Yoshimizu S, Kakushima N, Ohata K, Yamamoto H, Hara Y, Doyama H, Dohi O, Yamasaki Y, Ueyama H, Takimoto K, Kurahara K, Tashima T, Abe N, Nakayama A, Oda I, Yahagi N: Outcomes of endoscopic resection for superficial duodenal tumors: 10 years’ experience in 18 Japanese high volume centers.

Endoscopy, 2021. doi: 10.1055/a-1640-3236. Online ahead of print.PMID: 34496422 DOI: 10.1055/a-1640-3236.

29) Saito K, Nakai Y, Isayama H, Yamamoto R, Kawakubo K, Kodama Y, Katanuma A, Kanno A, Itonaga M, Koike K: A Prospective Multicenter Study of Partially Covered Metal Stents in Patients Receiving Neoadjuvant Chemotherapy for Resectable and Borderline Resectable Pancreatic Cancer: BTS-NAC Study. Gut Liver, 2021; 15: 135-141.

30) Takasaki Y, Ishii S, Shibuya T, Fujisawa T, Ushio M, Takahashi S, Ito K, Yamagata W, Suzuki A, Okahara K, Okawa Y, Ochiai K, Tomishima K, Nomura O, Haga K, Saito H, Nagahara A, Isayama H: Endoscopic ultrasound-guided antegrade procedures for managing bile duct stones in patients with surgically altered anatomy: Comparison with double-balloon enteroscopy-assisted endoscopic retrograde cholangiography (with video). Dig Endosc, 2021; 33: 1179-1187.

31) Hakuta R, Kogure H, Nakai Y, Kawakami H, Maguchi H, Mukai T, Iwashita T, Saito T, Togawa O, Matsubara S, Hayashi T, Maetani I, Ito Y, Hasebe O, Itoi T, Hanada K, Isayama H: Unilateral versus Bilateral Endoscopic Nasobiliary Drainage and Subsequent Metal Stent Placement for Unresectable Malignant Hilar Obstruction: A Multicenter Randomized Controlled Trial. J Clin Med, 2021; 10: E206.

32) Midorikawa H, Aiba M, Lebowitz A, Taguchi T, Shiratori Y, Ogawa T, Takahashi A, Takahashi S, Nemoto K, Arai T, Tachikawa H: Confirming validity of The Fear of COVID-19 Scale in Japanese with a nationwide large-scale sample. PLoS One, 2021; 16: e0246840.

33) Naitoh I, Kamisawa T, Tanaka A, Nakazawa T, Kubota K, Takikawa H, Unno M, Masamune A, Kawa S, Nakamura S, Okazaki K: Clinical characteristics of immunoglobulin IgG4-related sclerosing cholangitis: Comparison of cases with and without autoimmune pancreatitis in a large cohort. Dig Liver Dis, 2021; S1590-8658: 00061-X.

34) Saito T, Nakai Y, Mizuno S, Isayama H, Sasahira N, Kanai S, Noguchi K, Sato T, Ishigaki K, Hakuta R, Saito K, Hamada T, Takahara N, Kogure H, Koike K: Long-term outcome of endotherapy for pancreatic stones by using a dedicated pancreatic basket catheter. J Gastroenterol Hepatol, 2021; 36: 2424-2431.

35) Watanabe T, Nakai Y, Mizuno S, Hamada T, Kogure H, Hirano K, Akamatsu N, Hasegawa K, Isayama H, Koike K: Prognosis of primary sclerosing cholangitis according to age of onset. J Hepatobiliary Pancreat Sci, 2021; 28: 1115-1120.

36) Kawano F, Yoshioka R, Gyoda Y, Ichida H, Mizuno T, Ishii S, Fujisawa T, Imamura H, Mise Y, Isayama H, Saiura A: Laparoscopic cholecystectomy after endoscopic trans-papillary gallbladder stenting for acute cholecystitis: a pilot study of surgical feasibility. BMC Surg, 2021; 21: 184.

37) Kogure H, Nakai Y, Isayama H: Reply to Phillpotts and Webster. Endoscopy, 2021; 53: 560.

38) Ishigaki K, Nakai Y, Sasahira N, Sugimori K, Kitamura K, Iwai T, Matsubara S, Shimura S, Itoi T, Ryozawa S, Ushio J, Doi S, Imazu H, Maetani I, Isayama H: A prospective multicenter study of endoscopic ultrasound-guided fine needle biopsy using a 22-gauge Franseen needle for pancreatic solid lesions. J Gastroenterol Hepatol, 2021; 36: 2754-2761.

39) Angsuwatcharakon P, Kulpatcharapong S, Moon JH, Ramchandani M, Lau J, Isayama H, Seo WD, Maydeo A, Wang HP, Nakai Y, Ratanachu-Ek T, Bapaye A, Hu B, Devereaux B, Ponnudurai R, Khor C, Kongkam P, Pausawasdi N, Ridtitid W, Piyachaturawat P, Khanh PC, Dy F, Rerknimitr R: Consensus guidelines on the role of cholangioscopy to diagnose indeterminate biliary stricture. HPB (Oxford), 2021; S1365-182X: 00156-8.

40) Fujisawa T, Joshi BH, Takahashi S, Takasaki Y, Suzuki A, Ito K, Ochiai K, Tomishima K, Ishii S, Puri RK, Isayama H: IL-13Rα2 Is a Biomarker of Diagnosis and Therapeutic Response in Human Pancreatic Cancer. Diagnostics (Basel), 2021; 11: 1140.

41) Kogure H, Kato H, Kawakubo K, Ishiwatari H, Katanuma A, Okabe Y, Ueki T, Ban T, Hanada K, Sugimori K, Nakai Y, Isayama H: A Prospective Multicenter Study of "Inside Stents" for Biliary Stricture: Multicenter Evolving Inside Stent Registry (MEISteR). J Clin Med, 2021; 10: 2936.

42) Tomishima K, Ishii S, Fujisawa T, Yatagai N, Kabemura D, Sato S, Amano N, Murata A, Tsuzura H, Sato S, Matsumoto K, Shimada Y, Genda T, Nagahara A, Isayama H: Does restricting fluid volume impact post-ERCP pancreatitis in patient with heart disease? Saudi J Gastroenterol, 2021; 27: 355-360.

43) Iwashita T, Ogura T, Ishiwatari H, Nakai Y, Iwata K, Mukai T, Shimizu M, Isayama H, Yasuda I, Itoi T: Utility of dedicated bougie dilator for a 0.018-inch guidewire during EUS-guided biliary drainage: A multi-center retrospective cohort study. J Hepatobiliary Pancreat Sci, 2021. Online ahead of print.

44) Ochiai K, Fujisawa T, Ishii S, Suzuki A, Saito H, Takasaki Y, Ushio M, Takahashi S, Yamagata W, Tomishima K, Hisamatsu T, Isayama H: Risk Factors for Stent Migration into the Abdominal Cavity after Endoscopic Ultrasound-Guided Hepaticogastrostomy. J Clin Med, 2021; 10: 3111.

45) Kiyanagi A, Fujisawa T, Ishii S, Tomishima K, Takasaki Y, Suzuki A, Ushio M, Takahashi S, Yamagata W, Okawa Y, Ochiai K, Saito H, Isayama H: Usefulness of Routine Plain CT the Day After an Interventional EUS Procedure. Saudi J Gastroenterol, 2021; 27: 275-282.

46) Tomishima K, Ishii S, Fujisawa T, Ikemura M, Ota H, Kabemura D, Ushio M, Fukuma T, Takahashi S, Yamagata W, Takasaki Y, Suzuki A, Ito K, Saito H,

Nagahara A, Isayama H: Duration of Reduced CA19-9 Levels Is a Better Prognostic Factor Than Its Rate of Reduction for Unresectable Locally Advanced Pancreatic Cancer. Cancers (Basel), 2021; 13: 4224.
47) Kuwai T, Tamaru Y, Kusunoki R, Yoshida S, Matsuzawa T, Isayama H, Maetani I, Shimada M, Yamada T, Saito S, Tomita M, Koizumi K, Shiratori T, Enomoto T, Saida Y: Long-term outcomes of standardized colonic stenting using WallFlex as a bridge to surgery: A multicenter prospective cohort study. Dig Endosc, 2021. Online ahead of print.
48) Hamada T, Iwashita T, Saito T, Shiomi H, Takenaka M, Isayama H, Yasuda I, Nakai Y: Disconnected pancreatic duct syndrome and outcomes of endoscopic ultrasound-guided treatment of pancreatic fluid collections: Systematic review and meta-analysis. Dig Endosc, 2021. Online ahead of print.
49) Isayama H: Pancreato-biliary endoscopy: History of endoscopic biliary drainage. Dig Endosc, 2021. Online ahead of print.
50) Sasaki T, Yoshida S, Isayama H, Narita A, Yamada T, Enomoto T, Sumida Y, Kyo R, Kuwai T, Tomita M, Moroi R, Shimada M, Hirata N, Saida Y: Short-Term Outcomes of Colorectal Stenting Using a Low Axial Force Self-Expandable Metal Stent for Malignant Colorectal Obstruction: A Japanese Multicenter Prospective Study. J Clin Med, 2021; 10: 4936.
51) Satoi S, Takahara N, Fujii T, Isayama H, Yamada S, Tsuji Y, Miyato H, Yamaguchi H, Yamamoto T, Hashimoto D, Yamaki S, Nakai Y, Saito K, Baba H, Watanabe T, Ishii S, Hayashi M, Kurimoto K, Shimada H, Kitayama J: Synopsis of a clinical practice guideline for pancreatic ductal adenocarcinoma with peritoneal dissemination in Japan; Japan Peritoneal Malignancy Study Group. J Hepatobiliary Pancreat Sci, 2021. Online ahead of print.
52) Hisanaga T, Hidaka I, Sakaida I, Nakayama N, Ido A, Kato N, Takikawa Y, Inoue K, Shimizu M, Genda T, Terai S, Tsubouchi H, Takikawa H, Mochida S: Analysis of the safety of pretransplant corticosteroid therapy in patients with acute liver failure and late-onset hepatic failure in Japan. JGH Open, 2021; 5: 428-433.
53) Sato S, Amano N, Sato S, Kita Y, Ikeda Y, Kabemura D, Murata A, Yatagai N, Tsuzura H, Shimada Y, Genda T: Elevated serum tyrosine concentration is associated with a poor prognosis among patients with liver cirrhosis. Hepatol Res, 2021; 51: 786-795.
54) Sato S, Tsuzura H, Kita Y, Ikeda Y, Kabemura D, Sato S, Amano N, Yatagai N, Murata A, Shimada Y, Genda T: Post-treatment serum Wisteria floribunda agglutinin-positive mac-2-binding protein level is a useful predictor of hepatocellular carcinoma development after hepatitis C virus eradication. JGH Open. 2021; 5: 1203-1209.
55) Nakayama N, Uemura H, Uchida Y, Imai Y, Tomiya T, Terai S, Yoshiji H, Genda T, Ido A, Inoue K, Kato N, Sakaida I, Shimizu M, Takikawa Y, Abe M, Abe R, Chayama K, Hasegawa K, Inui A, Kasahara M, Ohira H, Tanaka A, Takikawa H, Mochida S: Nationwide survey for patients with acute-on-chronic liver failure occurring between 2017 and 2019 and diagnosed according to proposed Japanese criteria. J Gastroenterol, 2021; 56: 1092-1106.
56) Asaoka D, Takeda T, Inami Y, Abe D, Shimada Y, Matsumoto K, Ueyama H, Matsumoto K, Komori H, Akazawa Y, Osada T, Hojo M, Nagahara A: Association between the severity of constipation and sarcopenia in elderly adults: A single-center university hospital-based, cross-sectional study. Biomed Rep, 2021; 14: 2.
57) Sato S, Tsuzura H, Kita Y, Ikeda Y, Kabemura D, Sato S, Amano N, Yatagai N, Murata A, Shimada Y, Genda T: Hepatitis B Surface Antigen Decline during Sofosbuvir and Ribavirin Therapy in Hepatitis B Inactive Carriers Who Were Co-infected with Hepatitis C. Intern Med, 2021; 60: 3569-3572.
58) Hojo M, Ueda K, Takeda T, Akazawa Y, Ueyama H, Shimada Y, Asaoka D, Nagahara A: The relationship between *Helicobacter pylori* infection and reflux esophagitis and the long-term effects of eradication of *Helicobacter pylori* on reflux esophagitis. Therap Adv Gastroenterol, 2021; 14: 17562848211059942.
59) Ishikawa Y, Sato N, Tsukinaga S, Uchiyama K, Koido S, Ishikawa D: Long-term outcomes of antibiotic combination therapy for ulcerative colitis. Ther Adv Chronic Dis, 2021; 12: 20406223211028790.
60) Fukuo Y, Shibuya T, Ashizawa K, Ito K, Saeki M, Fukushima H, Takahashi M, Nomura K, Okahara K, Haga K, Akazawa Y, Nomura O, Ogura K, Okubo H, Nagahara A: Plasmablastic lymphoma of the small intestine in an HIV- and EBV-negative patient. Intern Med, 2021; 60: 2947-2952. doi: 10.2169/internalmedicine.6837-20. Epub 2021 Mar 29.
61) Okubo H, Ando H, Ishizuka K, Morishige JI, Ikejima K, Shiina S, Nagahara A: Impact of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of lenvatinib in patients with hepatocellular carcinoma. J Pharmacol Sci, 2022; 148: 6-13. doi: 10.1016/j.jphs.2021.08.011. Epub 2021 Sep 1.
62) Ikemura M, Tomishima K, Ushio M, Takahashi S, Yamagata W, Takasaki Y, Suzuki A, Ito K, Ochiai K, Ishii S, Saito H, Fujisawa T, Nagahara A, Isayama H: Impact of the Coronavirus Disease-2019 Pandemic on Pancreaticobiliary Disease Detection and Treatment. J Clin Med, 2021; 10: 4177. doi: 10.3390/jcm10184177.
63) Atsukawa M, Tsubota A, Kondo C, Toyoda H, Nakamuta M, Takaguchi K, Watanabe T, Hiraoka A, Uojima H, Ishikawa T, Iwasa M, Tada T, Nozaki A, Chuma M, Fukunishi S, Asano T, Ogawa C, Abe H, Kato K, Hotta N, Shima T, Matsuura K, Mikami S, Tachi Y, Fujioka S, Okubo H, Shimada N, Tani J, Morishita A, Hidaka I, Moriya A, Tsuji K, Akahane

T, Okubo T, Arai T, Kitamura M, Morita K, Kawata K, Tanaka Y, Kumada T, Iwakiri K: KTK49 Liver Study Group. Time-course changes in liver functional reserve after successful sofosbuvir/velpatasvir treatment in patients with decompensated cirrhosis. Hepatol Res, 2021. doi: 10.1111/hepr.13739. Online ahead of print.

64) Okubo H, Ando H, Nakadera E, Ikejima K, Shiina S, Nagahara A: Levocarnitine Supplementation Suppresses Lenvatinib-Related Sarcopenia in Hepatocellular Carcinoma Patients: Results of a Propensity Score Analysis. Nutrients, 2021; 13: 4428. doi: 10.3390/nu13124428.

65) Heissig B, Salama Y, Osada T, Okumura K, Hattori K: The Multifaceted Role of Plasminogen in Cancer. Int J Mol Sci, 2021; 22: 2304.

66) Ogawa T, Ogaki K, Mori Y, Kamo H, Uchiyama A, Kamagata K, Nagaoka M, Hattori N: Neuronuclear and Neuromelanin-Sensitive Imaging for Acquired Hepatocerebral Degeneration with Parkinsonism. Mov Disord Clin Pract, 2021; 8: 464-468.

67) Tateishi R, Matsumura T, Okanoue T, Shima T, Uchino K, Fujiwara N, Senokuchi T, Kon K, Sasako T, Taniai M, Kawaguchi T, Inoue H, Watada H, Kubota N, Shimano H, Kaneko S, Hashimoto E, Watanabe S, Shiota G, Ueki K, Kashiwabara K, Matsuyama Y, Tanaka H, Kasuga M, Araki E, Koike K; LUCID study investigators: Hepatocellular carcinoma development in diabetic patients: a nationwide survey in Japan. J Gastroenterol, 2021; 56: 261-273.

68) Kondo Y, Iwasa M, Kawaratani H, Miyaaki H, Hanai T, Kon K, Hirano H, Shimizu M, Yoshiji H, Okita K, Koike K: Proposal of Stroop test cut-off values as screening for neuropsychological impairments in cirrhosis: A Japanese multicenter study. Hepatol Res, 2021; 51: 674-681.

69) Kosar K, Cornuet P, Singh S, Lee E, Liu S, Gayden J, Sato T, Freyberg Z, Arteel G, Nejak-Bowen K: WNT7B Regulates Cholangiocyte Proliferation and Function During Murine Cholestasis. Hepatol Commun, 2021; 5: 2019-2034.

70) Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, Akuta N, Yoneda M, Iwasa M, Yoneda M, Otsuka M, Tamaki N, Kogiso T, Miwa H, Chayama K, Enomoto N, Shimosegawa T, Takehara T, Koike K: Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. J Gastroenterol, 2021; 56: 951-963.

71) Yin E, Fukuhara T, Takeda K, Kojima Y, Fukuhara K, Ikejima K, Bashuda H, Kitaura J, Yagita H, Okumura K, Uchida K: Anti-CD321 antibody immunotherapy protects liver against ischemia and reperfusion-induced injury. Sci Rep, 2021; 11: 6312.

72) Tokushige K, Ikejima K, Ono M, Eguchi Y, Kamada Y, Itoh Y, Akuta N, Yoneda M, Iwasa M, Yoneda M, Otsuka M, Tamaki N, Kogiso T, Miwa H, Chayama K, Enomoto N, Shimosegawa T, Takehara T, Koike K: Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. Hepatol Res, 2021; 51: 1013-10285.

73) Kawaratani H, Sawai H, onishi M, Kogiso T, Shimada N, Uojima H, Nakajima T, Matsumoto N, Ikejima K, Ishikawa T, Terai S, Motoyama H, Komori A, Hirashima N, Saito S, Eguchi Y, Nojima M, Kawai Y, Tateyama M, Yoshiji H, Tanaka Y: A genome-wide association study identifying SVEP1 variant as a predictor of response to tolvaptan for cirrhotic ascites. Liver Int, 2021 Dec; 41: 2944-2953.

〈Reviews〉

1) Eguchi S, Egawa H, Eguchi H, Uehira T, Endo T, Genda T, Shinoda M, Hasegawa K, Shimamura T, Tsukada K, Hara T, Nakao K, Yatsuhashi H, Yotsuyanagi H, Natsuda K, Soyama A, Hidaka M, Hara T, Takatsuki M: Indications and waiting list priority for deceased donor liver transplantation in HIV/HCV co-infected hemophilic patients in Japan through contaminated blood product. Hepatol Res, 2021; 51: 909-914.

〈Books〉

1) Fujisawa T, Isayama H, Ishii S, Ushio M, Takahashi S, Yamagata W, Takasaki Y, Suzuki A, Ito K, Ochiai K, Saito H: Management of Pancreatic Cancer and Cholangiocarcinoma. Springer, 2021, 313-324.

Diagnostic Imaging and Interventional Oncology

〈Original Articles〉

1) Okubo H, Ando H, Nakadera E, Ikejima K, Shiina S, Nagahara A: Levocarnitine Supplementation Suppresses Lenvatinib-Related Sarcopenia in Hepatocellular Carcinoma Patients: Results of a Propensity Score Analysis. Nutrients, 2021; 13: 4428.

2) Uchino K, Tateishi R, Wake T, Kinoshita MN, Nakagomi R, Nakatsuka T, Minami T, Sato M, Enooku K, Nakagawa H, Shiina S, Koike K: Radiofrequency Ablation of Liver Tumors in Patients on Antithrombotic Therapy: A Case-Control Analysis of over 10,000 Treatments. Journal of Vascular and Interventional Radiology, 2021; 32: 869-877.

3) Goto M, Sakamoto K, Kawano S, Munakata S, Kawai M, Ishiyama S, Sugimoto K, Takahashi M, Kojima Y, Tomita N, Saeki H, Shiina S: A case of simultaneous abdominal wall metastasis of hepatocellular carcinoma with long-term relapse-free survival after laparoscopic resection. International Cancer Conference Journal, 2021; 10: 217-221.

4) Kudo M, Izumi N, Kokudo N, Sakamoto M, Shiina S, Takayama T, Tateishi R, Nakashima O, Murakami T, Matsuyama Y, Takahashi A, Miyata H, Kubo S: Report of the 21st Nationwide Follow-up Survey of Primary Liver Cancer in Japan (2010-2011). Hepatology Research, 2021; 51: 355-405.

5) Nakagomi R, Tateishi R, Mikami S, Wake T, Kinoshita MN, Nakatsuka T, Minami T, Sato M, Uchino K,

Enooku K, Nakagawa H, Asaoka Y, Shiina S, Koike K: Infectious complications related to radiofrequency ablation of liver tumors: The role of antibiotics. PLoS One, 2021; 16: e0259641.

6) Kaibori M, Yoshii K, Kashiwabara K, Kokudo T, Hasegawa K, Izumi N, Murakami T, Kudo M, Shiina S, Sakamoto M, Nakashima O, Matsuyama Y, Eguchi S, Yamashita T, Takayama T, Kokudo N, Kubo S: Impact of hepatitis C virus on survival in patients undergoing resection of intrahepatic cholangiocarcinoma: Report of a Japanese nationwide survey. hepatology research, 2021; 51: 890–901.

7) Kawaguchi Y, Hasegawa K, Hagiwara Y, De Bellis M, Famularo S, Panettieri E, Matsuyama Y, Tateishi R, Ichikawa T, Kokudo T, Izumi N, Kubo S, Sakamoto M, Shiina S, Takayama T, Nakashima O, Murakami T, Vauthey JN, Giuliante F, De Carlis L, Romano F, Ruzzenente A, Guglielmi A, Kudo M, Kokudo N: Effect of Diameter and Number of Hepatocellular Carcinomas on Survival After Resection, Transarterial Chemoembolization, and Ablation. American Journal of Gastroenterology, 2021; 116: 1698–1708.

8) Kanzaki H, Chiba T, Ao J, Koroki K, Kanayama K, Maruta S, Maeda T, Kusakabe Y, Kobayashi K, Kanogawa N, Kiyono S, Nakamura M, Kondo T, Saito T, Nakagawa R, Ogasawara S, Suzuki E, Ooka Y, Muroyama R, Nakamoto S, Yasui S, Tawada A, Arai M, Kanda T, Maruyama H, Mimura N, Kato J, Zen Y, Ohtsuka M, Iwama A, Kato N: The impact of FGF19/FGFR4 signaling inhibition in antitumor activity of multi-kinase inhibitors in hepatocellular carcinoma. Sci Rep, 2021; 11: 5303.

9) Ao J, Chiba T, Shibata S, Kurosugi A, Qiang N, Ma Y, Kan M, Iwanaga T, Sakuma T, Kanzaki H, Kanayama K, Kojima R, Kusakabe Y, Nakamura M, Saito T, Nakagawa R, Kondo T, Ogasawara S, Suzuki E, Muroyama R, Kato J, Mimura N, Kanda T, Maruyama H, Kato N: Acquisition of mesenchymal-like phenotypes and overproduction of angiogenic factors in lenvatinib-resistant hepatocellular carcinoma cells. Biochem Biophys Res Commun, 2021; 549: 171–178.

10) Kusakabe Y, Chiba T, Oshima M, Koide S, Rizq O, Aoyama K, Ao J, Kaneko T, Kanzaki H, Kanayama K, Maeda T, Saito T, Nakagawa R, Kobayashi K, Kiyono S, Nakamura M, Ogasawara S, Suzuki E, Nakamoto S, Yasui S, Mikata R, Muroyama R, Kanda T, Maruyama H, Kato J, Mimura N, Ma A, Jin J, Zen Y, Otsuka M, Kaneda A, Iwama A, Kato N: EZH1/2 inhibition augments the anti-tumor effects of sorafenib in hepatocellular carcinoma. Sci Rep, 2021; 11: 21396.

＊ 11) Iino Y, Maruyama H, Mikata R, Yasui S, Koroki K, Nagashima H, Awatsu M, Shingyoji A, Kusakabe Y, Kobayashi K, Kiyono S, Nakamura M, Ohyama H, Sugiyama H, Sakai Y, Chiba T, Kato J, Tsuyuguchi T, Kato N: Percutaneous two-dimensional shear wave elastography for diagnosis of pancreatic tumor. Diagnostics (Basel), 2021; 11: 498.

12) Ao J, Chiba T, Kanzaki H, Kanayama K, Shibata S, Kurosugi A, Iwanaga T, Kan M, Sakuma T, Qiang N, Ma Y, Kojima R, Kusakabe Y, Nakamura M, Kobayashi K, Kiyono S, Kanogawa N, Saito T, Nakagawa R, Kondo T, Ogasawara S, Suzuki E, Nakamoto S, Muroyama R, Tawada A, Kato J, Kanda T, Maruyama H, Kato N: Serum Angiopoietin 2 acts as a diagnostic and prognostic biomarker in hepatocellular carcinoma. J Cancer, 2021; 12: 2694–2701.

13) Sato Y, Tamura K, Mori S, Tai, Dar-In; Tsui, Po-Hsiang; Yoshida K, Hirata S, Maruyama H, Yamaguchi T: Fatty liver evaluation with double-Nakagami model under low resolution conditions. Jpn. J. Appl. Phys, 60, SDDE06 (2021)

14) Koroki K, Kanogawa N, Maruta S, Ogasawara S, Iino Y, Obu M, Okubo T, Itokawa N, Maeda T, Inoue M, Haga Y, Seki A, Okabe S, Koma Y, Azemoto R, Atsukawa M, Itobayashi E, Ito K, Sugiura N, Mizumoto H, Unozawa H, Iwanaga T, Sakuma T, Fujita N, Kanzaki H, Kobayashi K, Kiyono S, Nakamura M, Saito T, Kondo T, Suzuki E, Ooka Y, Nakamoto S, Tawada A, Chiba T, Arai M, Kanda T, Maruyama H, Kato J, Kato N: Posttreatment after Lenvatinib in Patients with Advanced Hepatocellular Carcinoma. Liver Cancer, 2021; 10: 473–484.

15) Atsukawa M, Tsubota A, Kondo C, Uchida-Kobayashi S, Takaguchi K, Tsutsui A, Nozaki A, Chuma M, Hidaka I, Ishikawa T, Iwasa M, Tamai Y, Tobari M, Matsuura K, Nagura Y, Abe H, Kato K, Suzuki K, Okubo T, Arai T, Itokawa N, Toyoda H, Enomoto M, Tamori A, Tanaka Y, Kawada N, Takei Y, Iwakiri K: A novel noninvasive formula for predicting cirrhosis in patients with chronic hepatitis C. PLoS One, 2021; 16: e0257166. doi: 10.1371/journal.pone.0257166. eCollection 2021.

16) Shirono T, Koga H, Niizeki T, Nagamatsu H, Iwamoto H, Shimose S, Nakano M, Okamura S, Noda Y, Kamachi N, Kuromatsu R, Ogo E, Torimura T: Usefulness of a novel transarterial chemoinfusion plus external-beam radiation therapy for advanced hepatocellular carcinoma with tumor thrombi in the inferior vena cava and right atrium: Case study. Cancer Reports, 2021; e1539.

17) Iwamoto H, Niizeki T, Nagamatsu H, Ueshima K, Nomura T, Kuzuya T, Kasai K, Kooka Y, Hiraoka A, Sugimoto R, Yonezawa T, Ishihara A, Deguchi A, Arai H, Shimose S, Shirono T, Nakano M, Okamura S, Noda Y, Kamachi N, Sakai M, Suzuki H, Aino H, Matsukuma N, Matsugaki S, Ogata K, Yano Y, Ueno T, Kajiwara M, Itano S, Fukuizumi K, Kawano H, Noguchi K, Tanaka M, Yamaguchi T, Kuromatsu R, Kawaguchi A, Koga H, Torimura T, New Fp Study Group, Kurume Liver Cancer Study Group Of Japan: Survival Benefit of Hepatic Arterial Infusion Chemotherapy over Sorafenib in the Treatment of Locally

Progressed Hepatocellular Carcinoma. Cancers, 2021; 13: 646.

〈Reviews〉

1) Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, Toyoda H, Imai Y, Hiraoka A, Ikeda M, Izumi N, Moriguchi M, Ogasawara S, Minami Y, Ueshima K, Murakami T, Miyayama S, Nakashima O, Yano H, Sakamoto M, Hatano E, Shimada M, Kokudo N, Mochida S, Takehara T: Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer, 2021; 10: 181–223.
2) Maruyama H, Yamaguchi T, Nagamatsu H, Shiina S: AI-Based radiological imaging for HCC: Current status and future of ultrasound. Diagnostics (Basel), 2021; 11: 292.
3) Maruyama H, Shiina S: Collaterals in portal hypertension: anatomy and clinical relevance. Quant Imaging Med Surg, 2021; 11: 3867–3881.
4) Maruyama H, Shiina S: Connection between HPS and ACLF: a solution of chaos? Hepatol Int, 2021; 15: 1049–1052.

(Updated: May 25, 2023)

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編 集 後 記

最近、家族と親しい友人が立て続けに癌に罹患していることが判明した。二人ともこれまで健康にはほとんど問題がなく、元気が取り柄であったのが、一転して生命予後が心配になる状況に陥ったことで、まさかという気持ちが強く、現実として受け止めるまでに暫く時間がかかった。ネット上で国立がんセンターをはじめ、様々な機関が出している情報を探索した。5年生存率は、友人が約50％で、家族が10％未満。異なる部位の癌であり、治療法も異なるが各々の主治医からの説明を聞き、これまでの医学の進歩により私が医学生だった40年前に比べて様々な治療法が開発、普及されていることを知るとともに、それでも厳しい予後であることを知った。その一方で、癌の治療法のみならず、手術後の機能障害に対する取り組み、抗がん剤の副作用に対する取り組み等、患者のQOLを高める取り組みの進歩を実感した。一方の癌は、頑固な腹痛から発見に至ったが、生命予後は厳しいものの現在は適切なペインコントロールのお陰でQOLは高く保たれており、死ぬまで疼痛に苦しむというその癌特有とされていた以前の状況ではないことを知り、医学の進歩に深く感謝している。他方の癌は手術による大きな機能障害が課題であるが、医療者のみならず、工学系科学者の力により、機能回復に大きな進歩の兆しがあることが救いである。

今回の件で、医学ジャーナルの重要な役割である医療情報の発信という地道な活動の集積が医学・医療の進歩に果たしてきた役割を再確認するとともに、集団を対象とした知見を個人に当てはめる際の困難、ギャップを痛感した。

また、厳しい予後に直面する身近な命の残された未来を考えた時、これは当事者のみならず我々周囲の人間の残された人生の質についても問われていると感じている。Memento Moriという格言を思い返しながら、お互いに後悔のない日々を送ることを目指そうと考えている。

谷川　武
医学部公衆衛生学講座

イラスト作者より

こんなに暑い夏は、生れて初めてではないかと思う程の猛暑が続いています。少しでも涼しさを感じられるものと思い、水の入ったコップに足をつけて涼を取っている陶器製の猫を描いてみました。（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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抄　録

順天堂醫事雑誌
2023. 69(4), 360

私がみてきたこの国の精神医学
―40年間を振り返り―

鈴　木　利　人[1, 2)]

[1)]順天堂大学医学附属順天堂越谷病院
[2)]順天堂大学大学院医学研究科精神・行動科学

私は 1982 年に筑波大学医学専門学群を卒業し，同大学精神医学教室に入局しました．当時の国内の精神医学会は反精神医学の社会的風潮や精神科病院での入院患者への暴力事件報道により，精神医療における倫理意識が厳しく問われることとなり精神医学の臨床研究を行うには難しい環境にありました．このようなことから私のキャリアの前半の 20 年間は筑波大学で研鑽を積みましたが，そこでは主に統合失調症の動物モデルを対象とした基礎研究を取り組みました．統合失調症の発症に関して，当時ドパミン過剰仮説が有名でしたが脳内ドパミン神経伝達系の異常だけではなくそれに関連する神経ペプチドの変化にも注目し，さらに研究を発展させて興奮性（グルタミン酸神経系）・抑制性（GABA 神経系）アミノ酸神経系の神経伝達の異常についても検討しました．

2002 年 4 月，順天堂大学越谷病院に診療科長として赴任し，後半の 20 年間を順天堂大学で臨床活動を中心として活動してきました．M5 学生の臨床実習や研修医の臨床教育，精神科専門医の養成などをはじめ，多くの医局員の指導に携わるとともに，1 日外来患者数 350 名，年間入退院 500 名というメンタルクリニックの診療科を管理運営するようになりました．一方で，2010 年以降周産期メンタルヘルスに関する活動に携わり生涯のライフワークとなりました．2018 年に日本周産期メンタルヘルス学会の理事長を拝命し，周産期メンタルヘルスのガイドラインを作成して国内の周産期メンタルヘルス医療の向上に努めました．

キーワード：統合失調症動物モデル，順天堂越谷病院，周産期メンタルヘルス，ガイドライン

この抄録は，順天堂醫事雑誌 69 巻 4 号，p284–292，2023 掲載の『A Personal Historical Perspective on Psychiatry in Japan During the Last 4 Decades』の和文抄録です．

抄　録

順天堂醫事雑誌
2023. 69(4), 361

血液内科医としての私の40年のキャリア
―臨床上の課題に直面し、研究を変える～糖脂質から治療抵抗性まで―

野　口　雅　章

順天堂大学医学部附属浦安病院血液内科

私が1983年に順天堂大学医学部を卒業してから約40年が経った．卒業後5年間は東京大学生化学教室で糖脂質の研究に従事していた．その後，糖脂質に関する論文を執筆し発表した．やがて，私は血液内科で働き始めた．卒業後17年目の2000年，私は順天堂大学浦安病院血液内科に唯一の常勤医師として勤務した．多くの入院患者を管理するために，私は夜遅くまで長時間労働しなければならなかった．当科のホームページに記載されているように，専門学会の会議で行われた227件の発表のうち，145件(64%)が研修医によるものだった．この期間中に，15 名の研修医が血液内科に入局した. 2015年には, 研修医による寄稿がJournal of Clinical Oncologyなどのインパクトファクターの高い学術誌に受理された．小川理事長のご支援もあり，2023年4月より本学特任教授として勤務することになった．現在，造血器悪性腫瘍の治療抵抗性機序に関して病理学的研究をし，論文化を目指している．最近，私は順天堂大学の学是である「仁」,「不断進歩」,「三無主義（性別, 国籍, 学歴による差別をしない)」という理念に深く感謝するようになった．皆様におかれましては，ご自身の健康に留意しながら，この理念のもと，今後ともご活躍いただければ幸いである．今後とも一層のご支援，ご協力を賜りますようお願い申し上げる．

キーワード： 糖脂質，研修医中心の専門学会発表，造血器腫瘍，治療抵抗性のメカニズム

この抄録は，順天堂醫事雑誌69巻4号，p293–299，2023掲載の『My 40–year Career as a Hematologist – Facing Clinical Challenges and Changing My Research –Focus from Glycolipids to Therapy Resistance –』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
1 か月以上 4 か月未満	10 万円
4 か月以上 7 か月未満	20 万円
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

HP：https://www.juntendo.ac.jp/journal/membership/benefit_plan.html
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以上

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