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Detection of Factors Related to the Development of Osteochondritis Dissecans in Youth Baseball Players Screening

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Abstract: On-field screening for 'elbow injury in baseball', a condition commonly seen in youth baseball players, was conducted over two years on 160 elementary school students in Ibaraki Prefecture, Japan. This on-field screening was conducted in collaboration with the Ibaraki Prefecture High School Baseball Federation. Pitchers, catchers, symptomatic players, and players who had previously experienced elbow pain were given a comprehensive evaluation that included a physical exam and ultrasound. Out of the 135 students who were successfully screened, 10 were diagnosed with osteochondritis dissecans of the humeral capitellum (OCD). Notably, seven among these were asymptomatic. This assessment identified limited range of motion and pain when extending their elbow as significant risk factors for OCD. An attempt at on-field screening for baseball elbow injuries in collaboration with the local baseball federation was introduced. The risk factors for OCD were identified. Considering these factors, more efficient screening will be possible in the next attempt.

Keywords: on-field screening; elbow injury in baseball; osteochondritis dissecans of the humeral capitellum

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1. Introduction

Elbow injuries related to baseball are broadly classified into medial, lateral, and posterior types. Osteochondritis dissecans of the humeral capitellum (OCD), a disease representative of the lateral type of elbow injury in baseball, is more common in schoolchildren aged 9–12 years [1–3]. If the condition becomes severe, it causes functional impairment to the extent that the player cannot continue to play baseball [4]. Therefore, it is of paramount importance to focus on the early identification and appropriate intervention for OCD in this demographic. Notably, OCD is an affliction that often begins with minimal or no symptoms, a factor that can lead to delayed medical attention and, consequently, a deterioration of the condition by the time treatment is sought. Therefore, proactive early screening initiatives are vital. They hold the potential for enabling conservative treatments that focus on the repair of the lesion, thereby preventing the escalation to more serious stages that could imperil a young player's ability to continue in the sport.

OCD involves the separation of a section of articular cartilage and the underlying subchondral bone, leading to varying degrees of sclerosis, fragmentation, and resorption [5,6]. OCD affecting the trochlea is less common, accounting for 2.5–7% of all elbow OCD lesions [6–8]. While the exact underlying mechanism remains unclear, one hypothesis points to the tenuous blood supply to the posteroinferior aspect of the lateral trochlea [9,10]. Overhead athletes experience repeated impingement when extending their elbows, which can

exacerbate blood flow disorders [11]. In recent years, on-field screening for baseball elbow injuries for elementary and junior high school students has been conducted throughout Japan [1–3,12–14]. Past reports have shown a variety of target age groups, ranging from elementary school students [1,2,12,14] to extending the target to junior high school students and beyond [3,13]. Ultrasonographic examinations are valued in these screenings and have even been conducted at ground level in some cases [2,12]. The size of each screening session varies widely from approximately 100 to 1000 individuals, depending on the region and the environment.

In this context, it has been noted that until now, no screenings for elbow injury in baseball have been conducted in our region (Ibaraki Prefecture). This was due to a lack of know-how and human resources. On the other hand, upon request from the Prefectural High School Baseball Federation, post-game medical checks began to be conducted. Through these checks, it was discovered that a significant number of elementary and junior high school students have experienced throwing-related issues. In Ibaraki Prefecture, elbow-injury-in-baseball on-field screening for elementary school students has been conducted at the same time as youth baseball lessons organized by the Ibaraki High School Baseball Federation since 2016. Considering the number of players and the fact that screenings have not been conducted so far, it is conceivable that initiating screenings in these unscreened regions could potentially detect previously unrecognized cases. Furthermore, conducting elbow injury screenings could raise community awareness about this issue.

This study aimed to evaluate the effectiveness of our prefecture's approach to diagnosing and managing elbow injury in baseball among school-aged athletes and to consider more efficient screening methods with regard to detecting factors related to the development of OCD.

2. Materials and Methods

2.1. Participants

The study involved 160 subjects, including pitchers, catchers, players showing symptoms of elbow pain, and players with a previous history of elbow pain from a total of 470 baseball players of elementary school students (50 teams in total) who participated in youth baseball lessons organized by the prefectural high school baseball federation over a two-year period from 2017 to 2018 (Figure 1). None of the players had a medical check-up two years in a row.

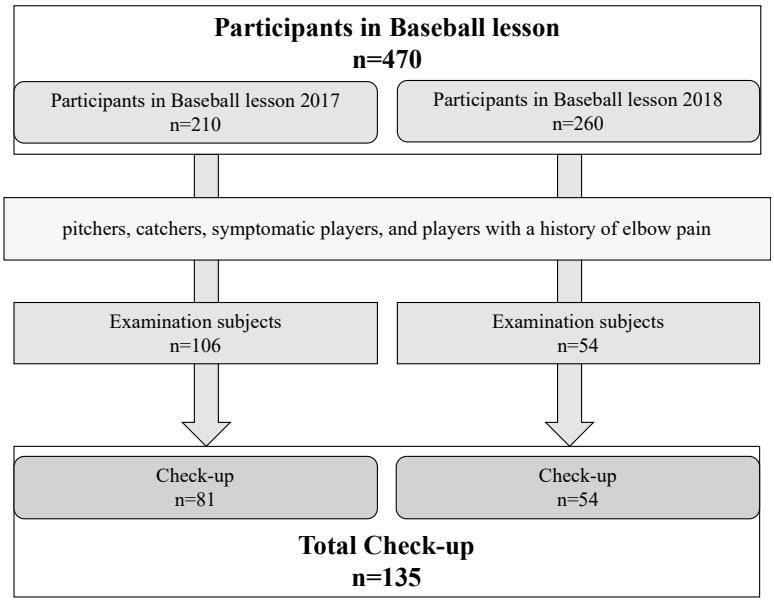

Figure 1. In total, 135 athletes were screened in two years.

2.2. Field Screening

First, the subjects were given a medical questionnaire in which they were asked to provide their name, team, position, and history of elbow pain. Physiotherapists and trainers then assessed the elbow for pain, limited motion, tenderness of the medial epicondyle, tenderness of the humeroulnar or humeroradial joint, tenderness of the olecranon, and instability with valgus stress tests at 30 degrees, 60 degrees, and 90 degrees of elbow flexion for both the throwing and non-throwing sides. The elbow joint was then examined by a physician using ultrasound to confirm the presence of OCD; the Okada's pattern classification was used to assess OCD [15] (Figure 2). The ultrasound examination focused solely on the lateral side of the elbow, checking both the short axis and the long axis. The equipment used for the ultrasound examination was a portable ultrasonography and an 11-MHz linear array transducer (SONIMAGE MX1, KONICA MINOLTA JAPAN Inc., Tokyo, Japan). The ultrasound examinations were performed by orthopedic surgeons with 3–10 years of experience. For the final analysis, the ultrasound images were interpreted by multiple physicians, including a specialist with over 20 years of experience in orthopedics. In this study, following the pattern classification, those with marginal irregularities were extracted, and the pattern S, which is typically not counted as OCD in a single examination, was also included as OCD for the purposes of this screening.

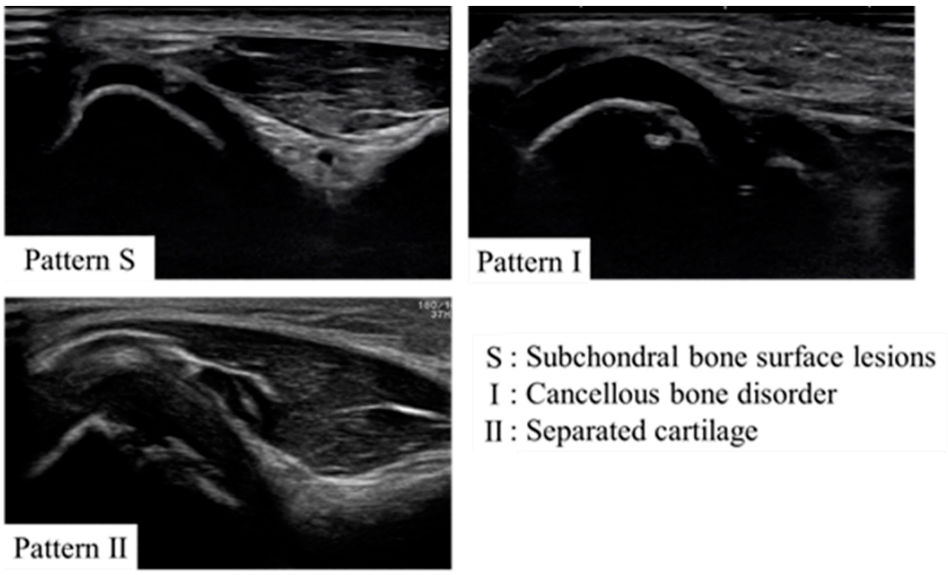

Figure 2. Characteristic ultrasound images of OCD extracted during the current screening are shown. This study followed Okada's pattern classification.

Players exhibiting severe pain, limited motion, or abnormal ultrasound findings were flagged for further investigation. The medical information form was prepared for a nearby medical facility, and they were instructed to undergo a secondary screening. In this study, if there were physical findings such as elbow pain, immediate aftercare instructions were provided on the spot. If the ultrasound examination indicated the presence of OCD, or if there was a suspicion of this condition, patients were advised to undergo a follow-up examination.

Additionally, an orthopedic surgeon lectured the participants and their parents about baseball-related elbow injuries (Figure 3). In the lecture, we primarily discussed medial and lateral elbow injuries in baseball. Furthermore, it was emphasized that screening tests are of utmost importance in the case of lateral elbow injuries which can lead to long-term absence from play. Early detection and prompt therapeutic intervention were highlighted as crucial factors.

Figure 3. A scene at the lecture on elbow injuries related to baseball.

2.3. Statistical Analysis

We analyzed the association between the physical findings and the occurrence of OCD, using the chi-square test. Individuals in the study were stratified into two distinct groups for analytical clarity. The subjects who did not exhibit OCD were labeled as Group N, while those diagnosed with OCD were categorized as Group O. Following the chi-square analysis, we proceeded with logistic regression analysis on the variables that exhibited a statistically significant difference.

3. Results

There were 160 subjects eligible for screening, of whom 135 completed the screening. The subjects were distributed across grades as follows: 43 were 12 years old, 47 were 11 years old, 21 were 10 years old, 17 were 9 years old, and 7 were 8 years old; the grade was unknown for four subjects. In terms of positions, 67 were pitchers, 28 were catchers, 23 were infielders, 15 were outfielders, and two were unknown positions. Of the total subjects who completed the screening, 31 warranted further evaluation. This determination was based on a combination of physical examination results and ultrasound findings, emphasizing the importance of a multi-faceted approach to screening. Within this subgroup necessitating additional investigation, 10 subjects, which constituted 7.4% of those who were screened, were diagnosed with OCD. The distribution by position was five pitchers, two catchers, two outfielders, and one position unknown. Within this subset of players, seven were identified as being asymptomatic. There was one symptomatic case in Pattern S (Case 4) and two symptomatic cases in Pattern 2 (Case 9, 10).

Those with complaints of elbow pain and joint tenderness were considered symptomatic. Physical examination revealed pain in 19 players, including 2 who were part of Group O. There was limited extension observed in eight players, half of whom belonged to Group O. Pain during extension was present in five players, with two being from Group O. Limited flexion was found in eight players, with two in Group O; pain on flexion was noted in four players, with none in Group O. Tenderness at the medial epicondyle was evident in 27 players, with 3 in Group O, while tenderness at the humeroradial joint was reported in 10 players, including 1 in Group O. Furthermore, tenderness at the olecranon

was found in five players, with one from Group O. The valgus stress test was positive at 30 degrees of elbow flexion in 13 players, with 1 in Group O; at 60 degrees, it was positive in 16 players, with none in Group O; and at 90 degrees, it was positive in 13 patients, with none in Group O (Table 1). Of those diagnosed with OCD, five exhibited pattern S, one had pattern 1, and four presented with pattern 2 (Figure 4).

Table 1. Results of physical examinations.

	Group N	Group O	*p* Value
Total number of players	125	10	
Throwing pain	17	2	0.58
Limited ROM in extension	4	4	<0.001
Extension pain	3	2	0.005
Limited ROM in flexion	4	0	0.57
Flexion pain	6	2	0.0501
Tenderness of medial epicondyle	24	3	0.41
Tenderness of brachial joint	9	1	0.74
Tenderness of olecranon	4	1	0.27
30° valgus stress test	12	1	0.97
60° valgus stress test	16	0	0.23
90° valgus stress test	13	0	0.28

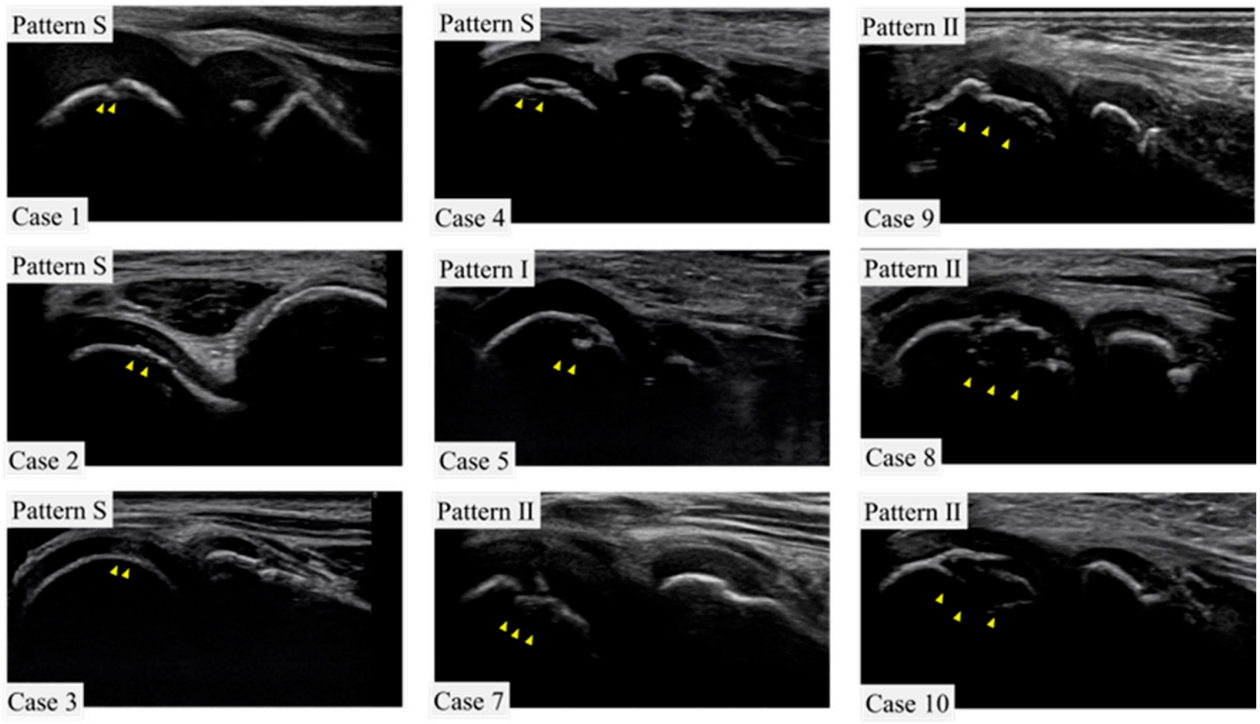

Figure 4. Ultrasound images of the lateral elbow for each case in this study. For one case (case 6), only the record was available, and the image was not preserved. Arrowheads indicate sites of OCD.

In our investigation, we employed the chi-squared test to assess the correlation between various physical signs and the incidence of osteochondritis dissecans (OCD). This statistical test indicated a notable correlation between the manifestation of OCD and specific physical symptoms: notably, individuals with OCD experienced significant pain upon elbow extension ($p = 0.005$), and there was a marked restriction in their range of motion during elbow extension ($p < 0.001$), highlighting these as potential indicators of the condition. Subsequently, we conducted a logistic regression analysis with the goal of establishing the presence of OCD as the dependent variable. In this model, we incorporated the physical findings that exhibited statistically significant differences in the chi-squared

test as the independent variables. Limited range of motion in elbow extension (OR, 19.42; CI, 3.61–104.60; $p < 0.001$) and pain in elbow extension (OR, 9.38; CI, 1.03–85.67; $p = 0.047$) were identified as significant risk factors for OCD (Table 2).

Table 2. Risk factors for developing OCD by logistic regression analysis.

	OR (95% CI)	*p* Value
Extension pain	19.42 (3.61–104.60)	<0.001
Limited ROM in extension	9.38 (1.03–85.67)	0.047

4. Discussion

There are approximately 200 youth baseball teams in Ibaraki Prefecture. Each year, approximately 25 teams from Ibaraki Prefecture participate in the screening, which is a small fraction of the nearly 200 youth baseball teams in the region. By examining a specific subset of positions within these teams, it is estimated that the participants in this screening represent about 3–5% of the total youth baseball population in the prefecture. One hundred and thirty-five patients were examined for on-field screening of elbow injuries related to baseball. It was found that ten of the subjects had OCD, seven of whom were asymptomatic. Twenty-five of the subjects did not join the screening because of team or family reasons.

In the youth baseball, the role of the pitcher is frequently assumed by those players who possess a rich background in the sport and can deliver pitches at high velocities. This group, as a result, is subject to substantial chronic elbow stress. The notably high occurrence rate of osteochondritis dissecans (OCD) detected in our study may be largely ascribed to our focus on central team players, namely pitchers and catchers, as well as those individuals reporting elbow discomfort. Existing research reports that the prevalence of elbow pain among young pitchers is roughly 26% [16]. It has been postulated that pitchers, due to the significant physical demands placed on their upper limbs during play, suffer from an increased rate of elbow pain in comparison to their counterparts in other positions [17–20]. With the objective of improving the effectiveness and precision of our screening process, we strategically confined our examination to pitchers, catchers, and those players with a documented history of elbow issues. The duration necessary for conducting this examination was approximately one and a half hours. Should we have extended this screening to encompass all members of the baseball teams, we estimate it would necessitate about four and a half hours—a threefold increase in time. Despite the overarching goal of a screening being to evaluate as comprehensive a player population as possible, we found that the examination proceeded efficiently, albeit within the constraints posed by limited staff and time availability. In a comparative light, our findings align with or diverge from other regional or international studies in intriguing ways. We selected the specific sampling method employed to target pitchers, catchers, and those experiencing elbow pain. Although this method efficiently detects OCD cases, it may have introduced a selection bias, warranting a discussion on the potential skewness in the data representation. It also raises the question of how universal screening across all player positions could reveal OCD prevalence more broadly.

Previous reports have shown that the prevalence of OCD in baseball elbow screening ranges from 1.2% to 3.4% [3,12,21]. In our study, the proportion of subjects who were deemed to require a secondary, more detailed screening was found to be 23.0%, which is substantially higher than previously reported. Moreover, a significant 7.4% of all the subjects examined were conclusively diagnosed with OCD by means of ultrasound evaluation. Both of these percentages represent high rates, which can be attributed to the specific selection of subjects for the study.

This investigation has determined that a limited range of motion during elbow extension and pain experienced upon extending the elbow are significant risk factors associated with OCD. Interestingly, there have been scant previous reports that make a connection between the specific pain during elbow extension and the onset of OCD, which positions

our findings as potentially groundbreaking. By bringing into focus the symptom of elbow extension pain—a facet that has not been extensively explored in prior research—we can potentially broaden the scope of candidates eligible for screening examinations. Should further research consolidate the link between elbow extension pain and OCD, this symptom could become a crucial criterion for advising against continued pitching. This advancement would not only contribute to medical guidelines but could also inform immediate, on-the-spot decisions to cease pitching activities at the field level, enhancing preventive measures and safeguarding the health of players.

Prevention, timely detection, and early intervention of elbow injuries in school-aged athletes are crucial to mitigating the onset of chronic elbow pain later in life. Baseball-related elbow injuries, especially osteochondritis dissecans (OCD), often present without symptoms in their initial stages. However, more severe cases may necessitate surgical intervention, raising concerns about potential lasting functional impairments. Consequently, conducting regular medical checkups focused on the elbow is essential for pre-empting injuries related to pitching. In the context of youth baseball, the early identification of OCD can pave the way for recovery through rest and non-invasive treatments. In contrast, delays in detection can lead to extended periods of discomfort and substantial challenges in maintaining pitching performance. Moreover, while a player might not experience pain during their youth baseball activities, it is possible that sudden pain could manifest as they progress in the sport. Under such circumstances, opportunities for repair through conservative treatment may diminish, often making surgical solutions a more common recourse. Therefore, implementing consistent screening protocols and promptly addressing any signs of discomfort are vital. These measures can facilitate the early detection and management of elbow injuries, thereby safeguarding the player's long-term engagement and performance in baseball.

In recent years, the scope and methods of elbow injury screenings in baseball have varied across regions. Iwame and Matsuura et al. have successfully promoted the importance of elbow screening over the years. They have now been able to secure a large population by holding the examinations in conjunction with youth regional baseball tournaments [22,23]. Kida et al. carry out baseball screenings for youth aged 12–18 during the off-season, synchronizing these examinations with regional baseball training camps to effectively capture a substantial participant base. Additionally, they conducted the program at the request of the Rubber Baseball Association, the Junior High School Baseball Federation, and the High School Baseball Federation. Over the course of a year, approximately 2500 participants, ranging from elementary to high school students, took part in these examinations [3]. They have successfully conducted large-scale elbow screenings by synchronizing the examinations with events such as regional tournaments and training camps, ensuring the participation of a broad range of young players. Sakata et al. conducted a pre-season medical check-up on 593 youth players aged 6–12 by the same examiner. Their findings indicated that pitchers had a significantly higher incidence of medial elbow injuries compared to other positions [18]. Tajika et al. screened 164 baseball players from regional youth baseball teams. They studied the occurrence of pain pre- and post-season, examining its correlation with physical changes and other clinical observations. Their findings revealed a significant relationship between pre-season body weight and the onset of elbow pain [24]. Otoshi et al. carried out baseball screenings post-season and studied the relationship between elbow pain and the off-season's length. Their findings indicated that a prolonged off-season corresponded to reduced occurrences of medial elbow pain. Yet, they observed no association between the off-season duration and the onset of OCD [1]. They have shown through pre- and post-season screenings that there is a correlation between the players' physical changes, the length of the off-season, and clinical symptoms. This information could be valuable for choosing future treatment and prevention strategies. Takata et al. conducted a screening of 1045 players with current or past elbow pain. There was a notable difference in the detection of OCD between those who received an ultrasound examination and those who did not, with a higher detection rate in the former group. Fur-

thermore, the ultrasound group also showed a higher follow-up examination attendance, underscoring the efficacy of ultrasound in such screenings [14]. Harada et al. conducted baseball screenings using ultrasound examinations and found that, out of 153 players, 35 presented with medial abnormalities detected by the ultrasound [12]. They demonstrated that the use of ultrasound allowed for more accurate detection of elbow abnormalities and promoted increased attendance at follow-up examinations. Outside of Japan, Holt et al. examined both elbows using MRI before and after the season to track any changes in condition. Their findings suggested that continuous play throughout the year significantly exacerbated MRI-detectable abnormalities [25]. However, given the use of MRI, this study goes beyond a simple screening examination. While baseball elbow screenings occur in many places, their scope and setting differ regionally. Similarly, proactive prevention approaches differ. When introducing screenings to previously underserved areas, challenges arise, such as selecting an appropriate venue, determining necessary staffing, and ensuring the availability of equipment like ultrasound machines. Given these screenings' nature, it is vital to swiftly and effectively assess many players to fulfill the screening's intended purpose.

In Ibaraki Prefecture, baseball lessons are held twice a year for members of the high school baseball teams. It was thought that the number of participants could be increased if the elbow screenings were held at the same time. The prefectural high school baseball federation readily agreed to the event because some players are unable to pitch in high school due to injuries sustained during their youth baseball days, and the event may lead to an increase in the future population of high school baseball players. Many of the youth baseball players also aspire to play in the Koshien National High School Baseball Championships. Therefore, we believed that the participation rate of screening would increase if they were encouraged by high school baseball players and coaches. As the new project, Ibaraki Prefecture also introduced elbow-injury-in-baseball on-field screening. It was not an easy task to raise awareness in areas where there had been no elbow injury screening in the past. We believe that holding the on-field screening at the same time as baseball lessons sponsored by the High School Baseball Federation helped to raise awareness. Unlike other sports, baseball has many federations. While soccer, athletics and other sports have their own federations under a larger federation, baseball, especially junior high school baseball, has many individual federations. This situation makes it difficult to hold health screenings. Therefore, we thought about collaborating with the High School Baseball Federation, to which most players belong if they continue to play baseball until their high school age. High school baseball is still very popular in Japan, and the prefectural high school baseball federations believe that popularization of preventive medicine will lead to the prevention of injuries. In addition, we also conducted on-field screening using mobile MRI [26]. When combined with mobile MRI, it may be possible to make a definitive diagnosis at the time of screening.

Limitations of this study include limited human resources and time. As this was a new project, the number of participants on the medical side was small and only pitchers, catchers, symptomatic players, and players with a history of elbow pain were included. Physical examination findings and ultrasound were used to diagnose OCD in this study. The study did not extend to the receipt and results of secondary medical examinations and did not reflect the results of X-rays and MRIs, which are commonly performed at secondary screening. In the future, we can increase the number of participants through the following: (1) by increasing the number of medical staff participants, and (2) arranging alternative dates for teams who are aware of the existence of OCD but are unable to participate due to tournaments, matches, and other reasons. In addition, it is necessary to increase cooperation with secondary health screening facilities. In this study, ultrasound examinations were performed by multiple examiners. While it was possible to evaluate OCD of the lateral epicondyle of the elbow, it should be noted that the ability to capture images may vary depending on the skill level of the examiner. Furthermore, while we used the Pattern classification, it should be noted that our study was designed as a screening procedure. At

present, we have not implemented changes in the treatment methods based on different Patterns. Future longitudinal studies with larger datasets might enable more definitive treatment decisions. It would also be desirable to evaluate medial epicondylitis of the elbow simultaneously and require even advanced proficiency in ultrasound examination techniques. There is a need for standardization in the methods of ultrasound imaging and evaluation across different examiners. Efforts have also been made to standardize the ultrasound examination method and improve the detection rate for medial baseball elbow injuries [27]. Moving forward, there will be a continuous search for more effective examination methods in elbow screenings.

The long-term implications of early OCD detection and treatment go beyond merely the physical realm. There is a socio-economic dimension considering the cost of treatment in advanced stages and a psychological facet given the mental strain on young players and their families. The value proposition of early interventions transcends the immediate health benefits and delves into the holistic wellbeing of the affected individuals and the community. Moreover, the success of this initiative in Ibaraki Prefecture beckons the exploration of it across other prefectures or even on a national scale. Follow-up studies, coupled with educational campaigns targeting coaches, players, and parents, can propagate the essence of early detection and preventive measures. The findings advocate for a structured framework within youth sports safety protocols, emphasizing regular health screenings and early interventions. The potential to translate these findings into actionable policies could significantly advance the overarching goal of fostering a safe and health-conscious sporting environment.

5. Conclusions

We have reported an attempt to conduct on-field screening of elbow injuries in the areas where elbow joint examinations have not been performed previously. Although we were able to introduce the system smoothly by cooperating with the local Higher-Level Baseball Federation, our efforts have shown that there is room for improvement. The prevalence of OCD was as high as 7.4% in the examination. The incidence was significantly higher than previous studies in other regions. This high rate may suggest that our on-field screening was efficient at catching cases that might have otherwise gone unnoticed. However, it may also be due to the limited population screened, indicating a need for broader and more frequent screening events. In addition, it is necessary to improve the efficiency of examinations. It was found that limited range of elbow extension and pain on elbow extension may be related to the onset of OCD. These findings not only align with existing medical knowledge but also pave the way for focused preventive measures. Collaborative efforts, integrating the expertise of medical professionals, the support of baseball federations, and the advancement in diagnostic technologies, form the cornerstone of evolving a sustainable and impactful preventive healthcare model within the youth baseball echo-screening system.

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The Effect of Axial Traction MRI on the Articular Cartilage Visibility in Thumb Carpometacarpal Arthritis

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Abstract

Objectives: Thumb carpometacarpal arthritis has a high incidence. However, the degree of damage to the cartilage has not been accurately assessed. The purpose of this study was to examine the effects of axial traction of the thumb carpometacarpal joint during magnetic resonance imaging (MRI) on the visibility of articular cartilage in patients with thumb carpometacarpal arthritis and to evaluate the articular cartilage defect using MRI findings.

Materials and methods: Forty-four patients with thumb carpometacarpal arthritis (14 males, 30 females) and a mean age of 67.3±8.6 years were classified according to Eaton Stages 1, 2, 3, and 4 in 2, 14, 24, and 4 patients, respectively. Axial traction MRI was performed with and without traction (3 kg) using 3-Tesla MRI (Siemens Magnetom Skyra) with a 3D T2* multiecho data imaging combination. The effectiveness of traction was verified using the joint space width before and after traction at five points (central, volar, dorsal, radial, and ulnar margins) and the original articular cartilage outline visibility classification (poor, intermediate, complete). The rate of remaining cartilage on each joint surface was also evaluated. Statistical significance was set at $p<0.05$ in this study.

Results: Joint space width increased significantly at all points with traction ($P<0.01$). The grade of articular cartilage outline visibility significantly improved from seven intermediate and 37 poor cases to 15 complete, 23 intermediate, and six poor cases ($P<0.01$). Significantly more articular cartilage remained in Stages 1-2 compared with Stages 3-4 arthritis of both articular surfaces ($P<0.01$ in first metacarpal, $P=0.01$ in trapezium).

Conclusion: Axial traction of the thumb increased the joint space width and improved articular cartilage visibility in the thumb carpometacarpal joint. Our results suggested that axial traction MRI can be used for noninvasive evaluation of articular cartilage defects in patients with thumb carpometacarpal arthritis and aid in selecting the optimal surgical procedure.

Categories: Orthopedics
Keywords: cartilage defect, articular cartilage, magnetic resonance imaging, axial traction, thumb carpometacarpal arthritis

Introduction

The thumb carpometacarpal joint is a saddle joint that connects the first metacarpal (MC1) and the trapezium and can be moved in multiple directions during daily activities such as pinching or grasping because of its anatomical characteristics [1,2]. The incidence of thumb carpometacarpal arthritis is high, occurring in >15% of adults aged >30 years and one-third of postmenopausal women, despite it being a non-weight-bearing joint [3-6]. Thumb carpometacarpal arthritis is usually diagnosed based on patient history, physical examination, and radiographs. The Eaton classification of thumb carpometacarpal arthritis is widely used to determine the staging and severity of this type of arthritis [7,8]. However, the degree of damage to the articular cartilage has not been accurately assessed, because the Eaton classification is based only on radiographs. One study reported that the intra- and inter-examiner reliabilities of this classification are low [9], whereas other studies have reported a poor correlation between clinical symptoms and intraoperative articular cartilage findings [10,11].

Magnetic resonance imaging (MRI) is widely used to evaluate articular cartilage damage. However, accurate articular cartilage evaluation of the thumb carpometacarpal joint is challenging because of its anatomical complexity and relatively small size compared to those of large joints such as the hip and knee. Although some reports have evaluated the articular cartilage of the thumb carpometacarpal joint using MRI [12-14], an

accurate method of evaluation has not yet been established because of the contact of the articular cartilage between the MC1 and the trapezium, as well as the underestimation of the degree of cartilage damage compared with other pathological findings [15].

To enhance the visibility of the articular cartilage, we performed an MRI while applying axial traction to the thumb carpometacarpal joint in healthy volunteers [16]. The joint space width of the thumb carpometacarpal joint was significantly increased in accordance with the traction weight, and the articular cartilage visibility of the thumb carpometacarpal joint was significantly improved by axial traction. This method of applying axial traction to improve the visualization of articular cartilage has also been previously used to observe other joints, such as the elbow and knee [17,18].

The aim of this study was to examine the effects of axial traction during MRI of the thumb carpometacarpal joint on the visibility of articular cartilage and to evaluate the remaining articular cartilage in patients with thumb carpometacarpal arthritis.

Materials And Methods

Study population

This study was approved by the institutional review board of the Tsukuba University Hospital Mito Clinical Education and Training Center, Ibaraki, Japan (No. R04-01), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

We enrolled 44 patients who visited our facility between April 2021 and October 2022 and were diagnosed with thumb carpometacarpal arthritis. Written informed consent was obtained from each patient after a thorough explanation of the objectives, methods, and expected complications.

Image acquisition

We used a 3-Tesla (3T) whole-body MRI system (Magnetom Skyra, Siemens Healthneers AG©, Munich, Germany) with a 4-channel 3T special purpose coil (Siemens Healthneers AG©, Munich, Germany). For the MRI sequence, a three-dimensional T2* multiecho data imaging combination (MEDIC) scan was used with the following parameters: slice thickness, 0.2 mm; slice gap, 0.15 mm; field of vision, 130 × 130 × 78 mm; matrix, 384 × 292; time to repeat, 20 ms; echo time, 11.0 ms; and flip angle, 25°. The required time, according to the protocol, was 5 min and 43 sec for each image. The patients were asked to lay supine on a table with their arms outstretched and their forearms pronated at the side of the body. The wrist and thumb were fixed with custom-made splints to standardize the limb position during the MRI examination. The hand under observation was centered parallel to the long axis of the gantry (Figure *1a*).

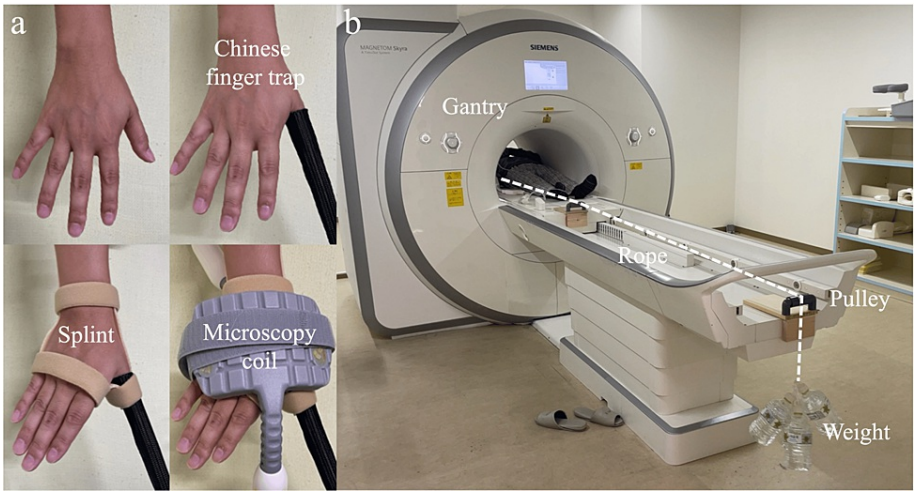

FIGURE 1: Application of axial traction during thumb carpometacarpal joint MRI

(a) The thumb is enclosed within a Chinese finger trap. Then, the wrist and thumb are fixed using a custom-made splint. Finally, the microscopy coil is placed around the wrist. (b) The Chinese finger trap is connected to the traction weight using a nonelastic rope routed through the pulley system.

Application of axial traction during MRI

The patient's thumb was enclosed within a Chinese finger trap (Allen® Sterile Mesh Finger Traps, AliMed, Inc., Massachusetts, USA) using a rope. After fixing the wrist and thumb using a splint to keep the thumb position at 40-degree abduction during traction, the other end of the rope was hung over the edge of the MR table via a pulley system and attached to non-magnetic traction weights (Figure *1b*). The MRI was initially performed without traction (no weight was used), followed by an MRI with traction. A traction weight of 3 kg was used based on our previous research [16].

Image analysis

We evaluated the effects of traction on the joint space width and articular cartilage outline visibility. In this study, the joint space width was defined as the space between opposing articular cartilages within the target joint. All MR images were independently evaluated by two orthopedic surgeons (with 15 and 10 years of clinical experience, respectively). All study images were interpreted on a workstation (Materialise Mimics, version 20.0; Materialise©, Leuven, Belgium), which was used to obtain the multiplanar reconstructed (MPR) images. Specifically, coronal and sagittal images were reconstructed parallel to the longitudinal axis of the first metacarpal region. The plane connecting the depressed portions of the distal metacarpal condyles with respect to the long axis was defined as coronal, and the plane perpendicular to the coronal plane was defined as sagittal. This procedure was performed by the first author for all the images. The images were initially enlarged, and the grayscale contrast was adjusted to optimize the visualization of the assessed structure. The images were then randomly numbered to minimize bias.

Measurement of the joint space width

Joint space width was measured on sagittal and coronal images at the center of the proximal articular surface of the first metacarpal bone as previously described [16]. On the sagittal image, the AB line, the line through both the volar (point A) and dorsal (point B) borders at the proximal articular surface of the first metacarpal bone; and the CD line, the line through both the volar (point C) and dorsal (point D) borders of the distal articular surface of the trapezium were drawn first. Subsequently, a perpendicular line was drawn at the center of the AB line and the intersection point of the articular surface of the first metacarpal bone was labeled as point E and the intersection point of the articular surface of the trapezium was labeled as point F. Furthermore, the intersection points of the perpendicular line drawn from points A and B to the CD line were labeled as points G and H. On the sagittal image, the following two lines were drawn: the IJ line, the line through the radial (point I) and ulnar (point J) borders of the proximal articular surface of the first metacarpal bone, and the KL line, the line through the radial (point K) and ulnar (point L) borders at the distal articular surface of the trapezium. Subsequently, the intersection points of the perpendicular lines drawn from points K and L to the IJ line were defined as points M and N. The distance between points E and F was defined as the center of the joint space width, those between points A and G and B and H were defined as the volar and dorsal joint space widths, and those between points I and M and J and N were defined as the radial and ulnar joint space widths, respectively (Figure *2*).

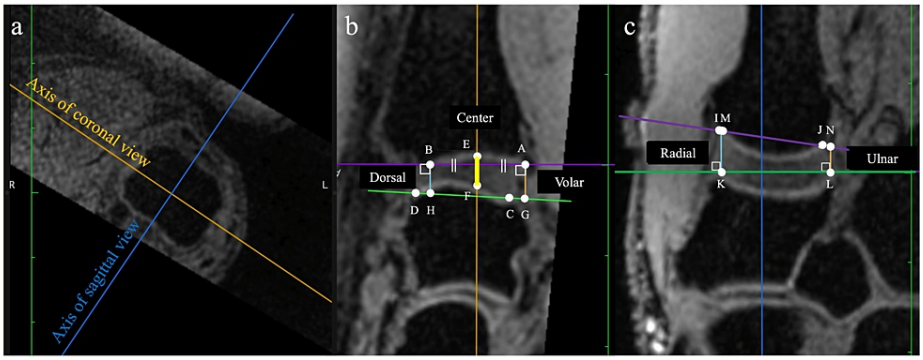

FIGURE 2: Definition of measurement points.

(a) The coronal and sagittal axes are defined using the axial plane at the first metacarpal bone head. (b) Sagittal image of first carpometacarpal joint. Distances E-F, A-G, and B-H were defined as the center, volar, and dorsal distances, respectively. (c) Coronal image at the first carpometacarpal joint. Distances K-M and L-N were defined as the radial and ulnar distances, respectively.

Assessment of the articular cartilage outline visibility

The articular cartilage outline visibility was graded using a three-grade scale as previously described [16]. Grade 2 (complete) occurred when 100% of the articular cartilage outline was clearly visible in the entire range when facing the opposing articular cartilage. Grade 1 (intermediate) occurred when ≥50% but <100% of the articular cartilage outline was clearly visible in the range when facing the opposing articular cartilage. Grade 0 (poor) occurred when the articular cartilage outline was visible in <50% of the entire range when

facing the opposing articular cartilage (Figure 3).

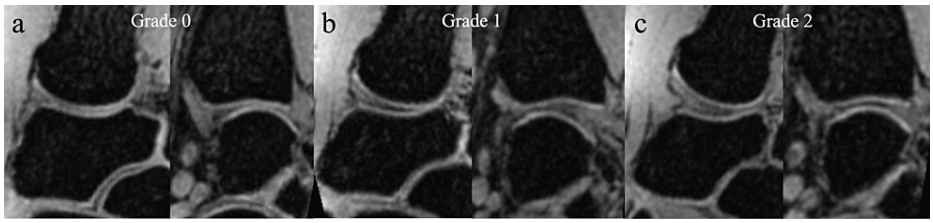

FIGURE 3: Articular cartilage outline visibility grade.

(a) Grade 0 (poor), (b) Grade 1 (intermediate), (c) Grade 2 (complete).

Measurement of the remaining cartilage rate

The rate of the remaining cartilage was evaluated using the same images on which joint space width was measured. On the sagittal and coronal images, the distance between the subchondral bone of the articular surface (line A-D) and the remaining cartilage (line A'-D') was measured both on the first metacarpal bone and trapezium. The rate of the remaining cartilage (%) was calculated by dividing the distance of the remaining cartilage by subchondral bone, and the average value of the sagittal and coronal images was used as the remaining cartilage rate of each bone (Figure 4).

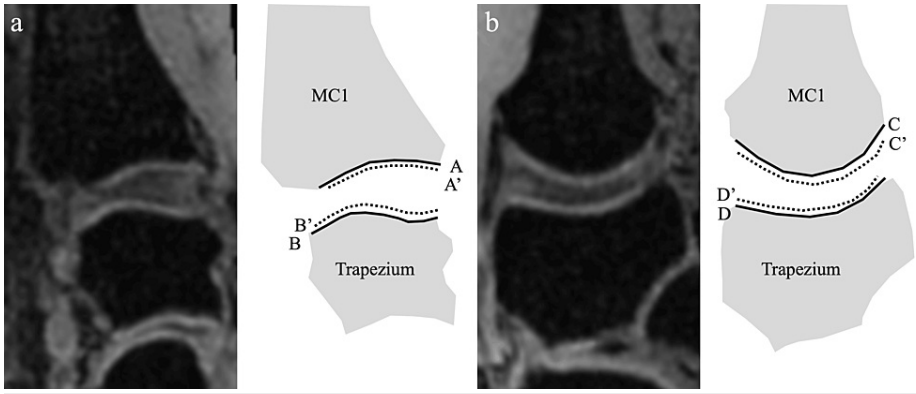

FIGURE 4: Calculation method of the remaining cartilage rate.

(a) Sagittal image, (b) coronal image. The remaining cartilage (%) was calculated by dividing the distance of remaining cartilage (A' to D') by subchondral bone (A to D). A, B, C, D: the distance of subchondral bone, A', B', C', D': the distance of remaining cartilage, MC1: first metacarpal.

Statistical analyses

GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA) was used for all statistical analyses. All data were tested for normal distribution using the Shapiro-Wilk test. None of the data on articular cartilage outline visibility, joint space width, and remaining cartilage rate followed a normal distribution, owing to the small sample size. Therefore, the Mann-Whitney and Friedman tests were used to assess the differences in joint space widths and articular cartilage outline visibility with and without traction and the differences in the remaining cartilage rate in Stages 1-2 and Stages 3-4 patients. Spearman's rank correlation coefficient was used to evaluate the correlation between the Eaton classification and articular cartilage visibility and changes in joint space width. Statistical significance was set at $p < 0.05$.

Results

The study population comprised 44 patients (men: 14, women: 30), with a mean age of 67.3 ± 8.6 (range, 50-82) years. According to the Eaton classification, 2 patients were in Stage 1, 14 in Stage 2, 24 in Stage 3, and 4 in Stage 4. There is no patient who suspended the MRI examination due to discomfort relating to traction.

The grades of articular cartilage outline visibility were intermediate in 7 and poor in 37 cases without traction, complete in 15, intermediate in 23, and poor in 6 cases with traction. The visibility of the articular cartilage outlines significantly improved with traction ($P<0.01$) (Figure 5). There was a significant correlation between the Eaton classification stage and the grade of articular cartilage visibility with traction ($r = -0.3096$, $P = 0.0409$), but no correlation was observed without traction ($r = -0.2890$, $P = 0.0571$).

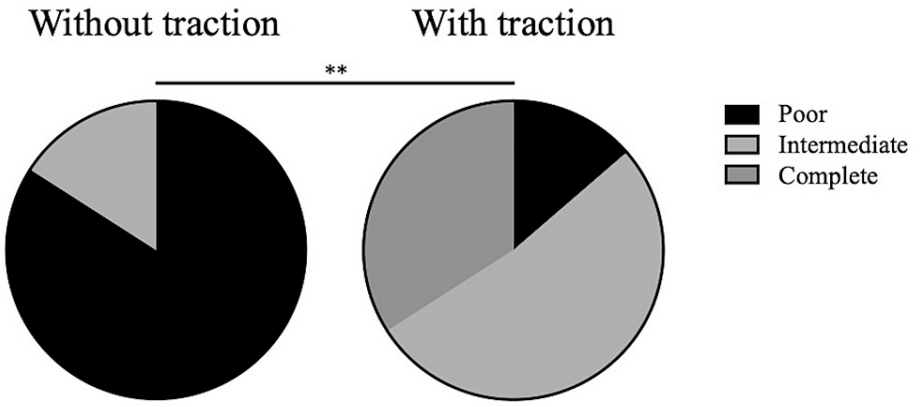

FIGURE 5: Visibility of the articular cartilage outlines.

The visibility is significantly improved by traction. ** P < 0.01.

The joint space width without/with traction was 1.02 ± 0.85/2.25 ± 1.04 mm in the center, 2.28 ± 1.41/3.83 ± 1.43 mm in the volar edge, 1.60 ± 1.77/2.67 ± 1.75 mm in the dorsal edge, 3.70 ± 1.61/4.93 ± 1.66 mm in the radial edge, and 1.43 ± 1.10/2.18 ± 1.39 mm in the ulnar edge. The joint space width increased significantly at all points with traction (P < 0.01) (Figure 6).

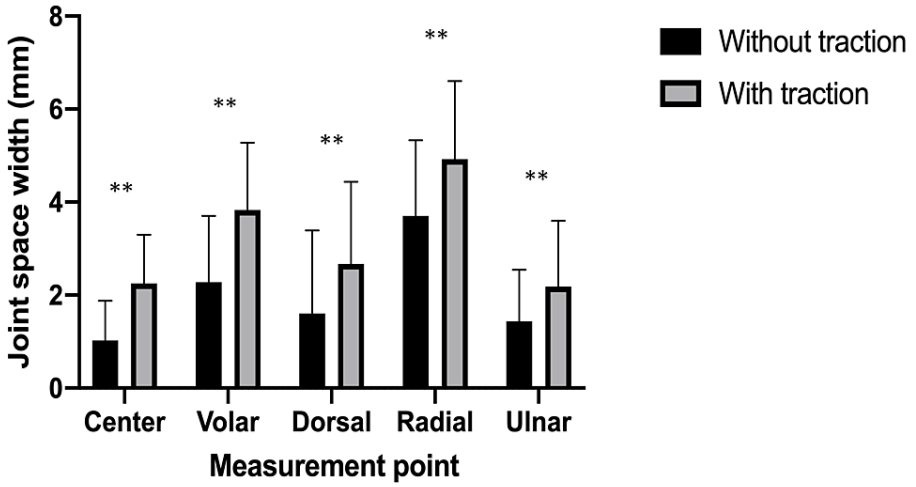

FIGURE 6: Joint space widths at each point (mean ± standard deviation).

Joint space widths significantly widened after axial traction at all points. ** P < 0.01.

The amount of change in joint space width before and after traction at each point was 1.23 ± 0.75 mm in the center, 1.55 ± 1.13 mm in the volar edge, 1.06 ± 1.11 mm in the dorsal edge, 1.22 ± 1.21 mm in the radial edge, and 0.75 ± 1.07 mm in the ulnar edge. No correlation between the Eaton classification stage and the change in joint space width was observed at any point (P=0.8801 at the center, 0.4884 at the volar, 0.6458 at the dorsal, 0.6080 at the radial, and 0.2983 at the ulnar edges). After comparing each point, the change in the ulnar edge was significantly smaller than that in the center (P<0.01), volar edge (P<0.01), and radial edge (P=0.02).

The rate of remaining cartilage on the first metacarpal surface was 51.0 ± 22.8% in Stages 1-2 and 32.5 ± 16.8% in Stages 3-4 (P<0.01). The rate of remaining cartilage on the trapezium surface was 46.5 ± 23.9% in Stages 1-2 and 26.8 ± 18.7% in Stages 3-4 (P=0.01) (Figure 7). However, when considering individual cases, large cartilage defect (>50%) was observed in four Stages 1-2 patients (25.0% of all Stages 1-2 patients), and >50% cartilage remained intact in three Stages 3-4 patients (10.7% of all Stage 3-4 patients).

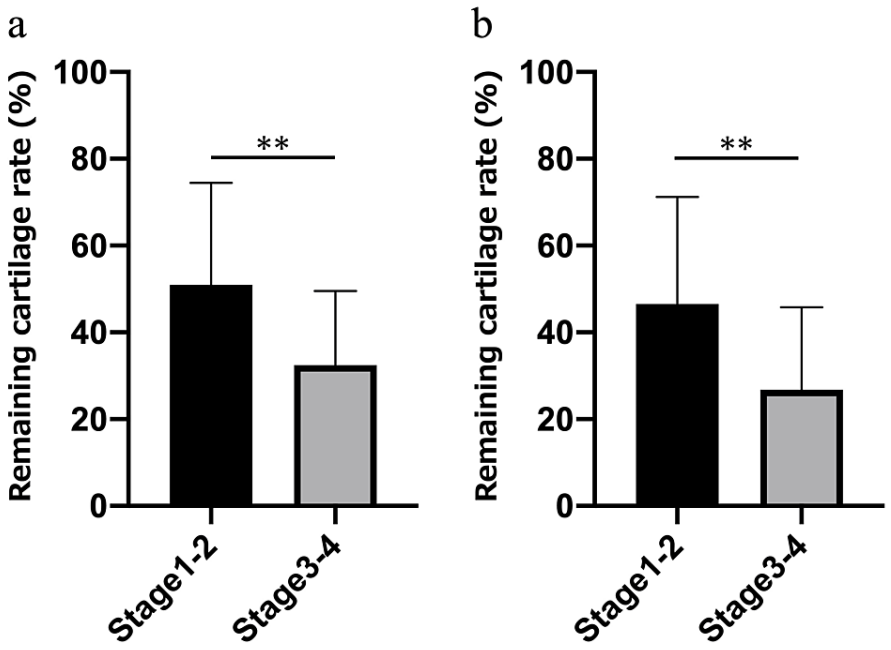

FIGURE 7: Remaining cartilage rate on sagittal and coronal images.

(a) Sagittal image; (b) coronal image. The presence of cartilage remained significant in Eaton Stages 1-2. ** P<0.01.

Discussion

Our results showed that the visibility of the cartilage outline of the thumb carpometacarpal joint on MRI was significantly better when axial traction was applied to the thumb in patients with thumb carpometacarpal arthritis, similar to that in healthy volunteers. The rate of remaining cartilage was significantly higher in patients in the early Eaton stages.

Various surgical procedures have been reported on thumb carpometacarpal arthritis [19]. For patients with mild osteoarthritic changes (Eaton classification Stages 1-2), ligament repair, arthroscopic synovectomy, and first metacarpal osteotomy are generally selected for joint-sparing surgery; whereas for patients with advanced osteoarthritic changes (Eaton classification Stages 3-4), ligament reconstruction with or without tendon interposition, arthrodesis, and artificial joint replacement are generally selected as non-joint-sparing surgery. Although the clinical outcomes of each surgical procedure are generally good [20], some joint preservation surgeries have achieved good symptomatic improvement even in patients with advanced osteoarthritic changes on plain radiographs [21,22]. In the present study, although the articular cartilage defect was significantly larger in patients with Eaton Stages 3-4, the cartilage remained >50% intact in 10% of those patients. The change in load distribution due to the first metacarpal osteotomy is one of the mechanisms used to reduce pain in patients with thumb carpometacarpal arthritis [23,24]. We believe that if the residual articular cartilage can be evaluated preoperatively, joint-sparing surgery can be performed more aggressively even in progressive cases. Thus, articular cartilage evaluation using axial traction MRI has the potential to be useful for surgeons in selecting less-invasive surgical procedures. We also believe that joint-sparing surgery is preferable for younger patients or those involved in heavy labor, although the risk of osteoarthritic progression exists even after long-term joint-sparing surgery.

In this study, the widening of the articular surface due to axial traction was significantly smaller on the ulnar side. The anterior oblique (or volar beak) and dorsoradial ligaments have been reported as key ligaments in thumb carpometacarpal arthritis [25-27]. These ligaments contribute to the stability of the radiodorsal side of the thumb carpometacarpal joint. According to the progression of thumb carpometacarpal arthritis, loosening of these ligaments related to radiodorsal instability of the thumb carpometacarpal joint may have caused the difference in joint space width between the measurement points by traction in this study. Although our results suggest that the degree of traction-induced widening of the joint space can be used to evaluate joint instability, which reflects ligament dysfunction, the sample size was insufficient for evaluating joint instability (ligament dysfunction). Future research efforts should aim to increase the sample size and verify whether axial traction MRI can evaluate ligament function and articular cartilage.

Badia et al. reported a treatment algorithm based on the intraoperative thumb carpometacarpal arthroscopy findings in 2006 [11]. Depending on the degree of articular cartilage damage or loss, joint-sparing or non-

joint-sparing surgery was selected for this algorithm. This algorithm is more innovative than the Eaton classification because it assesses articular cartilage damage and loss with higher accuracy before deciding on the surgical technique. However, several limitations have been encountered, including the inability to evaluate the articular cartilage preoperatively, invasiveness, and the need to decide the surgical technique intraoperatively. Our results demonstrate that axial traction MRI of the thumb carpometacarpal joint could be used to preoperatively evaluate the articular cartilage condition, which would allow the selection of the optimal surgical technique that reflects the articular cartilage condition, rather than depending on the Eaton classification.

This study has several limitations. First, the assessment of the rate of remaining cartilage was limited to a single slice of sagittal and coronal images in this study. Developing an evaluation method encompassing the whole joint surface, possibly using techniques such as 3D reconstruction, is necessary for a more accurate assessment of the articular cartilage condition in future studies. Second, the optimal traction weight was not evaluated in this study. While increasing the axial traction on the thumb with heavier weights might further widen the joint space and improve the articular cartilage outline visibility, this added traction may induce pain in these individuals. Compared with our previous result of the change in joint space width in healthy volunteers [16], there was no significant difference between 3 kg traction in patients with thumb carpometacarpal arthritis and 2 kg and 5 kg traction in healthy volunteers (Figure *8*). Thus, a 3 kg traction was considered sufficient to evaluate articular cartilage defects in the thumb carpometacarpal joint. Thirdly, this study did not verify whether articular cartilage was correctly detected by MRI. To evaluate the precision of detecting articular cartilage through axial traction MRI, a study comparing the consistency between MRI and arthroscopy findings is necessary for future research. Finally, the axial traction system used in this study could not control the rotational force on the carpometacarpal joint of the thumb. A slight twist caused by axial traction may have affected the measurement of the joint space widths at each point. Therefore, the addition of a system to control the rotational force during axial traction becomes imperative.

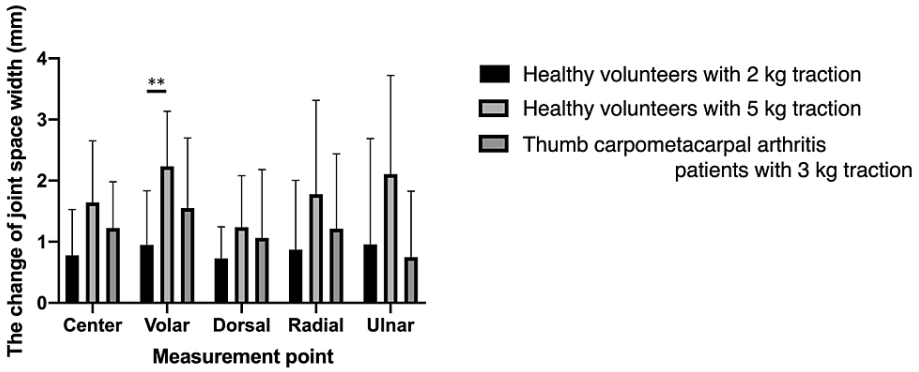

FIGURE 8: The change of joint space width between with and without traction.

There is no significant difference between 3 kg traction in thumb carpometacarpal arthritis patients and both 2 kg and 5 kg traction in healthy volunteers at any measurement point by two-way ANOVA with the Geissler-Green house correction. ** P < 0.01 between 2 kg and 5 kg traction in healthy volunteers by Tukey's multiple comparisons test.

Conclusions

Axial traction of the thumb increased the joint space width and improved the visibility of the articular cartilage of the thumb carpometacarpal joint on the MRIs of patients with thumb carpometacarpal arthritis.

Our results suggest that axial traction MRI can be used to noninvasively evaluate articular cartilage defects in patients with thumb carpometacarpal arthritis.

Axial traction MRI holds potential as an evaluation index for selecting the optimal surgical method in patients with thumb carpometacarpal arthritis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Akira Ikumi, Sho Kohyama

Acquisition, analysis, or interpretation of data: Akira Ikumi, Sho Iwabuchi, Takeo Mammoto, Takeshi Ogawa, Yuichi Yoshii, Masashi Yamazaki

Drafting of the manuscript: Akira Ikumi

Critical review of the manuscript for important intellectual content: Sho Iwabuchi, Sho Kohyama, Takeo Mammoto, Takeshi Ogawa, Yuichi Yoshii, Masashi Yamazaki

Supervision: Yuichi Yoshii

Disclosures

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Effect of Preoperative Oral Antibiotics and Mechanical Bowel Preparations on the Intestinal Flora of Patients Undergoing Laparoscopic Colorectal Cancer Surgery: A Single-Center Prospective Pilot Study

Monitoring Editor: Alexander Muacevic and John R Adler

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Abstract

Introduction: In the last few decades, considerable progress has been made in controlling surgical site infections (SSIs) using a combination of mechanical and oral antibiotic bowel preparation. However, the number of bacteria present after bowel preparation has not been clarified. In this study, we investigated the bacterial cultures of intestinal fluid samples from patients undergoing laparoscopic surgery for colorectal cancer after preoperative bowel preparation.

Methods: This prospective observational study was designed as a pilot study at a single center. We enrolled 25 consecutive patients who underwent laparoscopic surgery for colorectal cancer between March 2021 and February 2022 at our institution.

Results: The rate of bacterial culture positivity was 56.0%. The most abundant bacterium was *Escherichia coli* (44.0%). The positivity rates for *E. coli* on the right and left sides were 54.5% and 35.7%, respectively ($P = 0.60$). Moreover, there was a significant relationship between a low American Society of Anesthesiologists Physical Status score and *E. coli* positivity on the right side ($P = 0.031$). In the left-sided group, female sex and large tumor size were significantly associated with *E. coli* positivity ($P = 0.036$ and 0.049, respectively). Superficial SSI occurred in the patient in the left-sided group, but *E. coli* was negative.

Conclusion: This study emphasizes the importance of understanding intestinal fluid contamination and its relationship to infection risk. Future prospective multicenter studies should be conducted to determine the association between intestinal bacteria and different types of preoperative preparation.

Keywords: surgical site infection, laparoscopic surgery, intracorporeal anastomosis, colorectal cancer, bowel preparation

Introduction

Recently, the rapid development of laparoscopic colorectal cancer surgery has enabled surgeons to perform total intracorporeal anastomosis (IA) [1,2]. Colorectal cancer surgery is associated with a higher risk of surgical site infections (SSIs) than other gastrointestinal surgeries [3]. More than 100 trillion bacterial cells are present in the human gastrointestinal tract [4,5]. There has been an increasing research interest in SSIs, especially among surgeons performing IA [6]. Moreover, considerable attention has been paid to preoperative bowel preparations, such as mechanical bowel preparation (MBP) with laxatives and oral antibiotic bowel preparation (OABP) [7-9].

Previous studies have demonstrated the advantages of IA [2,6,10-12], but IA can cause unintended contamination of intestinal fluid during anastomosis, and these studies have not addressed the following points. First, although previous findings support the importance of IA over extracortical anastomosis (EA) in SSI control, the mechanism by which intestinal fluid is contaminated remains unclear. Second, even if surgeons carefully avoid contamination by intestinal fluid, the risk of contamination is not eliminated, and the characteristics of patients with bacterial contamination remain unclear.

In the last few decades, progress has been made in controlling SSIs by utilizing OABP and MBP [7,8,13]. Several recent studies have shown that SSIs, including intra-abdominal abscesses, are less common with IA than with EA [6,12]. Most SSIs after colorectal surgery are caused by Escherichia coli, Enterococcus faecalis, Bacteroides fragilis, Enterobacter cloacae, or Pseudomonas aeruginosa [14]. Thus, preoperative bowel preparation is performed before colorectal surgery [8,13]. The latest guidelines published by the World Health Organization [15], Enhanced Recovery After Surgery Society [16], Society of American Gastrointestinal and Endoscopic Surgeons [17], American Society of Colon and Rectal Surgeons [18], and American College of Surgeons [19] recommend a combination of MBP and OABP to reduce SSI risk.

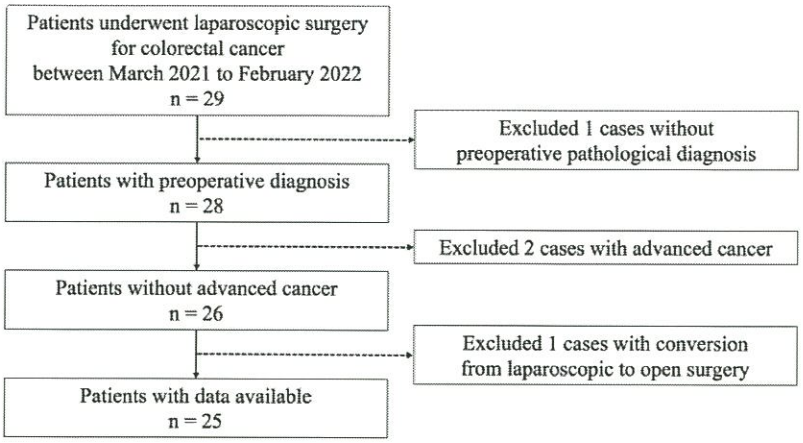
Thus, we hypothesized that a combination of MBP and OABP eliminates bacteria from the bowel lumen, but the effectiveness differs between right-sidedness and left-sidedness of the tumor. This would contribute to a decrease in the incidence of SSI due to unintended abdominal contamination. However, the number of bacteria remaining after the combination of bowel preparation has not been clarified in recent laparoscopic colorectal surgeries. In the present study, we investigated bacterial cultures of intestinal fluid samples from patients undergoing laparoscopic surgery for colorectal cancer after preoperative combinational bowel preparation with IA and EA. Furthermore, we analyzed the association between patient characteristics and bacterial cultures based on the sidedness of tumor location.

Materials and methods

Patient selection and study design

This prospective, observational study was designed as a pilot study at a single center. We enrolled consecutive patients who underwent laparoscopic surgery for colorectal cancer between March 1, 2021, and February 28, 2022, at Iwate Prefectural Chubu Hospital, Japan. The patient selection process is illustrated in Figure 1. The inclusion criteria were as follows: colon or rectal cancer, operation completed using laparoscopic surgery, age > 20 years, no distant metastasis, no invasion into surrounding organs, pathological diagnosis based on preoperative biopsy examination, and no use of antibiotics within one month. The exclusion criteria were as follows: no definite diagnosis of colon or rectal cancer, bowel obstruction with cancer, unresectable factors, preoperative chemotherapy administration, stent placement, and history of allergy or other adverse reactions to the antimicrobial agents used in this study. The study was conducted in accordance with the ethical standards proposed in the Declaration of Helsinki, 1964, and approved by the institutional ethical board of the Ethics Committee of Iwate Prefectural Chubu Hospital (approval 11000793). Written informed consent was obtained from the study participants.

Figure 1



Flow diagram depicting the selection of the study participants.

Preoperative bowel preparations

All patients underwent both MBP and OABP since 2020 at our institution as a standard practice in our hospital. OABP consisted of 500 mg metronidazole and 500 mg kanamycin after lunch and bedtime on the day before surgery. Intravenous cefmetazole (1 g) was administered every three hours during surgery. We used 24 mg of sennoside for right-sided colon cancer and 2 L of a polyethylene glycol solution for left-sided colorectal cancer.

Sample collection for intestinal fluid culture

Intestinal fluid samples were collected by swabbing the mucosal surface of the resected specimen around the tumor from the proximal to distal margin in the operating room after resection. Laboratory technicians who performed the culture tests were completely blinded to peri-

operative information, except for the location of the tumor. The technicians used both aerobic and anaerobic culture conditions. They also aimed to identify bacteria from the blinded samples.

Evaluation and quantification of cultural results

We classified the growth status of the identified organisms in the culture into five categories: 0 for no growth or minimal colony formation of only a few colonies in less than one-third of the plate, 1+ for less than one-third of the plate, 2+ for one-third to two-thirds of the plate, 3+ for more than two-thirds of the plate, and 4+ for the entire plate. The culture was defined as negative when the medium growth status was 0.

Clinical parameters

We evaluated the following clinical parameters to identify the risk factors for bacterial positivity after MBP and OABP: sex, age, tumor location, side of tumor location, body mass index, American Society of Anesthesiologists Physical Status (ASA-PS) classification, presence of a history of regular use of laxatives, current smoking, diabetes mellitus, anastomosis procedures, lymph node dissection, pathological differentiation, pathological Union for International Cancer Control (UICC) 8th edition TN factors and stages, tumor size, tumor markers (carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9), operative time, perioperative blood loss, hospitalization day, adverse effects of antibiotics, and postoperative complications (anastomotic leakage, intra-abdominal abscess, superficial SSI, and deep SSI).

Statistical analysis

We evaluated the association between the bacterial and clinical parameters. Categorical variables were analyzed using the chi-square and Fisher's exact tests. Continuous variables were analyzed using a two-sided t-test and Mann-Whitney U test for parametric and nonparametric data, respectively. We additionally stratified the patients into two groups depending on tumor location, considering the difference in bacteria on the side of the colorectal tumor location. JMP Pro version 17 (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. Statistical significance was defined as $P < 0.05$.

Results

Patient background

A total of 25 patients were enrolled in the study. The patient characteristics are summarized in Table 1. The median age was 67.0 years, 48.0% of the patients were female, and 56.0% of the tumors were located on the left side. The proportion of laxative users was 24.0%. Of the patients, 20.0% were anastomosed with IA, and 40.0% were anastomosed with a double-stapling system. The prevalence of superficial SSIs was 4.0%. No anastomotic leakage, deep SSI, or intra-abdominal abscess were observed.

Table 1

Characteristics of study participants

IQR; Interquartile range, SD; Standard deviation, ASA-PS; American Society of Anesthesiologists Physical Status, UICC; Union for International Cancer Control, CEA; Carcinoembryonic antigen, CA19-9; Carbohydrate antigen, SSI; Surgical site infection

Characteristics			
Age years, median [IQR]	67.0 [57.4–79.5]	Pathological differentiation, No. (%)	
Sex (Female/Male), No. (%)	12/13 (48.0/52.0)	Poor	1 (4.0)
Tumor location, No. (%)		Moderate	6 (24.0)
Cecum	5(16.0)	High	18 (72.0)
Ascending colon	5 (20.0)	UICC T (8th), No. (%)	
Transverse colon	2 (8.0)	1	10 (40.0)
Descending colon	2 (8.0)	2	7 (28.0)
Sigmoid colon	5 (20.0)	3	8 (32.0)
Rectum	7 (28.0)	UICC N (8th), No. (%)	
Sidedness (right/left), No. (%)	11/14 (44.0/56.0)	0	20 (80.0)
Body mass (index kg/m^2), mean±SD	23.1 ± 3.2	1	5 (20.0)
ASA-PS, No. (%)		Tumor size (mm), median [IQR]	25.0 (19.0–30.0)
1	7 (28.0)	CEA (ng/mL), median [IQR]	2.8 (1.9–4.7)
2	9 (36.0)	CA19-9 (U/mL), median [IQR]	7.3 (2.8–12.9)
3	6 (24.0)	Operative time (min)	
4	3 (12.0)	Intraoperative blooding (mL)	
Laxative, No. (%)	3 (12.0)	Postoperative hospitalized stay (days)	
Smoker, No. (%)	10 (40.0)	Adverse effect of oral antibiotics, No. (%)	0 (0.0)
Diabetes mellitus, No. (%)	2 (8.0)	Anastomotic leakage, No. (%)	0 (0.0)
Anastomosis, No. (%)		Superficial SSI, No. (%)	1 (4.0)
Extracortical	10 (40.0)	Deep SSI, No. (%)	0 (0.0)
Intracortical	5 (20.0)	Intraabdominal abscess, No. (%)	0 (0.0)
Double stapling system	10 (40.0)		
Lymph node dissection, No. (%)			

Results of microbial culture

Table 2 summarizes the culture results of the samples, and Table 3 summarizes the prevalence of the five major bacteria causing SSIs: Escherichia coli, Enterococcus faecalis, Bacteroides fragilis, Enterobacter cloacae, and Pseudomonas aeruginosa. The rate of bacterial culture positivity was 56.0%. There were no significant differences in sidedness. Further analysis revealed that the most abundant bacterium was E. coli (44.0%). The positivity rates of E. coli on the right and left sides were 54.5% and 35.7%, respectively. Enterococcus faecalis was detected in 21.4% and 9.1% of patients with left-sidedness and right-sidedness, respectively. However, this difference was not significant (P = 0.60). These findings indicated that E. coli was the predominant bacterial species on both sides.

Table 2

Identification of bacterial culture species and their colorectal locations

Location	Characteristic bacteria
Cecum	Bacillus, Bacteroides fragilis, Candida albicans, Escherichia coli, Klebsiella pneumonia, Serratia marcescens, Staphylococcus aureus, Streptococcus bovis
Ascending colon	Bacillus, Candida albicans, Enterobacter cloacae, Enterococcus faecalis, Enterococcus raffinosus, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Pseudomonas aeruginosa
Transverse colon	Bacillus, Escherichia coli, Klebsiella oxytoca, Pseudomonas aeruginosa, Streptococcus bovis
Descending colon	Enterococcus avium, Enterococcus faecalis, Escherichia coli, Klebsiella oxytoca, Morganella morganii, Pseudomonas aeruginosa, Streptococcus bovis
Sigmoid colon	Enterococcus faecalis, Klebsiella oxytoca, Streptococcus bovis
Rectum	Bacillus, Edward, Escherichia coli, Group G, Klebsiella oxytoca, Klebsiella pneumonia

Table 3

Positive rate of microbial culture: major risk species for surgical site infection

*P < 0.05 is statistically significant

Bacteria	Total	Right-sidedness	Left-sidedness	P-value
	No. (%)	No. (%)	No. (%)	
Any five bacteria	14/25 (56.0)	7/11 (63.6)	7/14 (50.0)	0.69
Escherichia coli	11/25 (44.0)	6/11 (54.5)	5/14 (35.7)	0.43
Enterococcus faecalis	4/25 (16.0)	1/11 (9.1)	3/14 (21.4)	0.60
Bacteroides fragilis	1/25 (4.0)	1/11 (9.1)	0/14 (0.0)	0.44
Enterobacter cloacae	1/25 (4.0)	1/11 (9.1)	0/14 (0.0)	0.44
Pseudomonas aeruginosa	2/25 (8.0)	1/11 (9.1)	1/14 (7.1)	1.00

Clinical factors for cultural positivity

To investigate the association between the clinical background of the patients and culture positivity for E. coli, we classified them into two groups: right and left sides (Table 4). There was a statistically significant relationship between low ASA-PS score and E. coli positivity on the right side (P = 0.031). However, no significant difference was observed between sexes and E. coli positivity (P = 0.57). In the left-sided group, female sex and large tumor size were significantly associated with E. coli positivity (P = 0.036 and 0.049, respectively). Superficial SSI occurred in the patient in the left-sided group, but E. coli was negative.

Table 4

Associations between Escherichia coli positivity and cohort characteristics

*P < 0.05 is statistically significant

IQR; Interquartile range, SD; Standard deviation, ASA-PS; American Society of Anesthesiologists Physical Status, UICC; Union for International Cancer Control, CEA; Carcinoembryonic antigen, CA19-9; Carbohydrate antigen, SSI; Surgical site infection

Characteristics	Right-sidedness			Left-sidedness		
	Positive (n = 6)	Negative (n = 5)	P-value	Positive (n = 5)	Negative (n = 9)	P-value
Age years, median [IQR]	73.5 [60.8–83.5]	82.0 [79.5–83.5]	0.15	54.0 [46.0–61.5]	60.0 [57.5–69.0]	0.066
Sex (Female), No. (%)	4 (66.7)	2 (40.0)	0.57	4 (80.0)	2 (22.2)	0.036*
Body mass index (kg/m2), mean±SD	22.0 ± 3.8	22.5±0.9	0.52	24.0 ± 2.4	23.7 ± 4.2	0.59
ASA-PS, No. (%)			0.031*			0.78
1	2 (33.3)	0 (0.0)		3 (60.0)	2 (22.2)	
2	3 (50.0)	1 (20.0)		1 (20.0)	4 (44.4)	
3	0 (0.0)	3 (60.0)		1 (20.0)	2 (22.2)	
4	1 (16.7)	1 (20.0)		0 (0.0)	1 (11.1)	
Laxative, No. (%)	0 (0.0)	2 (40.0)	0.12	1 (20.0)	1 (11.1)	1.00
Smoker, No. (%)	3 (50.0)	2 (40.0)	1.00	1 (20.0)	4 (44.4)	0.58
Diabetes mellitus, No. (%)	0 (0.0)	1 (20.0)	1.00	1 (20.0)	0 (0.0)	0.36
Lymph node dissection, No. (%)			1.00			1.00
D2	3 (50.0)	2 (40.0)		3 (60.0)	5 (55.6)	
D3	3 (50.0)	3 (60.0)		2 (40.0)	4 (44.4)	
Pathological differentiation, No. (%)			0.061			0.58
Poor	0 (0.0)	1 (20.0)		0 (0.0)	0 (0.0)	
Moderate	0 (0.0)	2 (40.0)		2 (40.0)	2 (22.2)	
High	6 (100)	2 (40.0)		3 (60.0)	7 (77.8)	
UICC (8th) Stage, No. (%)			0.89			0.49
1	3 (50.0)	3 (60.0)		4 (80.0)	5 (55.6)	
2	2 (33.3)	1 (20.0)		0 (0.0)	2 (22.2)	
3	1 (16.7)	1 (20.0)		1 (20.0)	2 (22.2)	
UICC T (8th), No. (%)			0.24			0.33
1	2 (33.3)	0 (0.0)		2 (40.0)	6 (66.7)	
2	2 (33.3)	4 (80.0)		1 (20.0)	0 (0.0)	
3	2 (33.3)	1 (20.0)		2 (40.0)	3 (33.3)	

Although we investigated the association between the clinical background of patients and culture positivity for any bacteria, no statistically significant relationships were observed (Table 5).

Table 5

Associations between any bacteria positivity and cohort characteristics

*P<0.05 is statistically significant

IQR; Interquartile range, SD; Standard deviation, ASA-PS; American Society of Anesthesiologists Physical Status, UICC; Union for International Cancer Control, CEA; Carcinoembryonic antigen, CA19-9; Carbohydrate antigen, SSI; Surgical site infection

Characteristics	Right-sidedness			Left-sidedness		
	Positive (n = 7)	Negative (n = 4)	P-value	Positive (n = 7)	Negative (n = 7)	P-value
Age years, median [IQR]	75.0 [67.0–83.0]	82.0 [78.8–83.8]	0.30	57.0 [47.0–64.0]	60.0 [58.0–70.0]	0.18
Sex (Female), No. (%)	4 (57.1)	2 (50.0)	0.82	4 (57.1)	2 (28.6)	0.59
Body mass (index kg/m^2), mean±SD	22.3 ± 3.5	22.2 ± 0.3	0.92	22.8 ± 2.9	24.9 ± 4.0	0.27
ASA-PS, No. (%)			0.44			0.55
1	2 (28.6)	0 (0.0)		3 (42.9)	2 (28.6)	
2	3 (42.9)	1 (25.0)		2 (28.6)	3 (42.9)	
3	1 (14.3)	2 (50.0)		2 (28.6)	1 (14.3)	
4	1 (14.3)	1 (25.0)		0 (0.0)	1 (14.3)	
Laxative, No. (%)	1 (14.3)	1 (25.0)	1.00	1 (14.3)	1 (14.3)	1.00
Smoker, No. (%)	4 (57.1)	1 (25.0)	0.55	3 (42.9)	2 (28.6)	1.00
Diabetes mellitus, No. (%)	1 (14.3)	0 (0.0)	1.00	1 (14.3)	0 (0.0)	1.00
Lymph node dissection, No. (%)			0.30			1.00
D2	4 (57.1)	1 (25.0)		4 (57.1)	4 (57.1)	
D3	3 (42.9)	3 (75.0)		3 (42.9)	3 (42.9)	
Pathological differentiation, No. (%)			0.31			1.00
Poor	0 (0.0)	1 (25.0)		0 (0.0)	0 (0.0)	
Moderate	1 (14.3)	1 (25.0)		2 (28.6)	2 (28.6)	
High	6 (85.7)	2 (50.0)		5 (71.4)	5 (71.4)	
UICC (8th) Stage, No. (%)			0.44			0.80
1	3 (42.9)	3 (75.0)		5 (71.4)	4 (57.1)	
2	2 (28.6)	1 (25.0)		1 (14.3)	1 (14.3)	
3	2 (28.6)	0 (0.0)		1 (14.3)	2 (28.6)	
UICC T (8th), No. (%)			0.44			0.35
1	2 (28.6)	0 (0.0)		3 (42.9)	5 (71.4)	
2	3 (42.9)	3 (75.0)		1 (14.3)	0 (0.0)	
3	2 (28.6)	1 (25.0)		3 (42.9)	2 (28.6)	

Discussion

We found that the culture positivity rate of the intestinal fluid samples was 56% after combination preparation, and most samples were positive for E. coli. Sex, tumor size, and ASA-PS scores were significantly associated with bacterial culture positivity. However, bacterial culture positivity was not associated with the occurrence of SSI. IA has been shown to reduce the risk of SSIs and intra-abdominal abscesses compared with EA [6,12]. While the combination of MBP and

OABP for preoperative bowel preparation minimizes the risk of SSIs, little is known about the number of bacteria present in the intestinal fluid after preoperative bowel preparation [7,8]. The present study was designed to identify the bacterial species in the intestinal fluid after MBP and OABP. We collected intestinal fluid for cultures during laparoscopic colorectal surgery.

As suggested in previous studies, we found that the characteristics of cancer patients, including sex, are related to the bacterial flora of the intestinal mucosa [20-24]. Previous studies have reported that the abundance of Bacteroides is related to physical activity in athletes and gait speed in healthy elderly women [25,26]. Another study reported a negative correlation between Enterobacteriaceae and gait speed in Parkinson's patients [27]. Furthermore, higher ASA-PS has been reported to be associated with resistance to certain antibiotics [14]. Hence, the ASA-PS score could be related to intestinal flora through many confounding factors. This may be because bacterial positivity did not affect the occurrence of SSIs.

We found that approximately 50% of intestinal fluid samples contained bacteria. To the best of our knowledge, no study has analyzed the culture of intestinal fluid after preoperative bowel preparation, as conducted in our study. In 1989, Sasaki et al. cultured 1 g of fecal samples after MBP and OABP [28]. They reported that MBP and OABP decreased the number of aerobic and anaerobic bacteria from 6.6±1.7 log10/g to 4.2±1.9 log10/g and 7.3±1.9 log10/g to 3.0±2.1 log10/g, respectively [28]. Approximately 24% of aerobic and 70% of anaerobic bacteria were below the detection limit [28]. Thus, considering these results, our results on the bacterial positivity rate after preparation are feasible. However, Sasaki et al. administered oral antibiotics at higher doses and for longer periods than those utilized by us herein. Therefore, our study is unique in that our preoperative preparations were consistent with the current real-world settings, suggesting that the current preparation is effective and safe.

Our study had several limitations. First, the sample size is small. Given that our findings were based on a limited number of patients, our results must be interpreted with caution. Although we could not make strong statements based on our research, we believe that patient characteristics can influence intestinal bacteria. Second, our study could not evaluate and compare the microbiomes without antibiotics. We need more data comparing the effects of antibiotics. Moreover, this study did not provide detailed data on bacterial identification. We investigated the bacterial culture positivity of intestinal fluid samples; however, recent studies on microbiomes have used 16S ribosomal RNA sequencing [29]. The obstruction and chemotherapy can influence these microbiomes. In this study, we excluded these patients to determine the patients' backgrounds. However, we need to investigate the microbiomes of these patients because recent advances in surgery enable us to perform minimally invasive surgery for these advanced patients. Further investigation that can reflect real-world clinical outcomes from a clinical perspective remains to be determined.

This study presents novel data on the bacterial characteristics found in the intestinal fluid of patients undergoing colorectal cancer surgery after MBP and OABP. Our findings can help advance the understanding of the influence of intestinal preparation and reduction of SSIs during IA. These can also give the fundamental data to optimize the appropriate MBP and OABP methods for colorectal cancer surgery. It may contribute to developing the strategy of preparation and reducing SSIs.

Conclusions

Our study provides insight into the risk of SSIs and the safety of IA. Despite these limitations, our study serves as a starting point for discussions regarding intestinal fluid contamination and SSI control. Our results suggest that higher ASA-PS and larger tumor size may be risk factors for bacterial positivity. However, appropriate preparation may allow us to perform IA safely. Future prospective multicenter studies should investigate the association between intestinal bacteria and various types of preoperative preparation. Additionally, further studies are required to validate our findings.

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Notes

The authors have declared that no competing interests exist.

Human Ethics

Consent was obtained or waived by all participants in this study. Institutional Review Board, the Ethics Committee of Iwate Prefectural Chubu Hospital issued approval 11000793. This study was performed in accordance with the ethical standards of the institutionally responsible committee on human experimentation and with the Helsinki Declaration. All patients provided written informed consent before enrolment in the study.

Animal Ethics

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

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ANTICANCER RESEARCH

Research Article Clinical Studies

Prognostic Impact of Preoperative Assessment of Muscle Mass and Strength in Surgically Resected Lung Cancer

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Abstract

Background/Aim: The association between resected non-small cell lung cancer (NSCLC) and long-term outcomes of muscle mass depletion and muscle weakness has also not been well documented. This study evaluated whether muscle mass depletion assessed by bioelectrical impedance analysis (BIA) and low muscle strength assessed by the peak expiratory flow rate as a percentage of predicted value (%PEFR) were associated with surgical outcomes in patients with resected NSCLC. Patients and Methods: This retrospective study included 219 patients with resected NSCLC between 2016 and 2021. The cutoff value for muscle mass depletion was according to guidelines, for low muscle strength, we defined by receiver operating characteristics analysis for recurrence-free survival (RFS). Survival analysis was performed, and postoperative outcomes were compared. Results: A total of 76 patients (34.7%) had muscle mass depletion, and 114 patients (52.1%) had low muscle strength. Muscle mass depletion and low muscle strength were independent poor prognostic factors for overall survival [hazard ratio (HR)=2.631, p=0.003; HR=1.983, p=0.044] and RFS (HR=3.120, p<0.001; HR=1.857, p=0.028) in multivariate analysis. Postoperative complication was associated with low muscle strength (p=0.009). Postoperative recurrence was associated with muscle mass depletion (p=0.03). Conclusion: Preoperative muscle mass depletion assessed by BIA and low muscle strength determined by %PEFR are worse prognostic factors after surgical resection for NSCLC. Our results may provide some important information for preoperative management.

Optimal Limb Position for the Stress Ultrasound Evaluation of Elbow Valgus Laxity in Baseball Players

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Background: The optimal limb position during stress ultrasound (SUS) evaluation of elbow valgus laxity has not been standardized.

Purpose: To compare 2 elbow positions (at 90° and 30° of flexion) and report which position method better represents the increased valgus laxity characteristics of baseball players.

Study Design: Controlled laboratory study.

Methods: Eighteen college baseball players with no history of elbow pain or elbow disorders who belonged to a college baseball club between April and November 2021 participated in this study. The medial elbow joint space (MEJS) was recorded by ultrasonography at rest and under valgus stress, and the difference in MEJS between the conditions was considered the valgus laxity. For all participants, the MEJS was recorded at 90° and 30° of elbow flexion. In the 90° of flexion position, the participant was positioned in the supine position with abduction and external rotation of the shoulder, and 2.5 kgf of valgus stress was applied proximally to the wrist. In the 30° of flexion position, the participant was positioned in the sitting position with abduction and external rotation of the shoulder, and 3.0 kgf of valgus stress was applied to the ulnar head. Valgus laxity on the throwing and nonthrowing sides was compared between the 2 elbow positions using paired *t* tests or Wilcoxon signed-rank tests after checking the normality.

Results: There was a significant difference in valgus laxity on the throwing side between the 90° and 30° of flexion positions (1.9 vs 1.1 mm, respectively; $P = .002$), whereas no significant difference between positions was seen on the nonthrowing side ($P = .06$).

Conclusion: SUS with the elbow flexed at 90° more clearly detected valgus laxity in the study participants than the 30° of flexion position.

Clinical Relevance: The quantitative evaluation of valgus laxity is important for baseball players to assess the risk of ulnar collateral ligament injury.

Keywords: stress ultrasound; evaluation; elbow valgus laxity; baseball players

In the baseball throwing motion, a large valgus stress is loaded on the throwing elbow joint from the late cocking phase to the acceleration phase.[7] This valgus stress is repeatedly loaded on the elbow with each throw, resulting in valgus laxity.[5,6,8,9,11,13,20] Excessive increase in valgus laxity is a reported risk factor for ulnar collateral ligament (UCL) injury among baseball players.[22] Hence, quantitative evaluation of valgus laxity is important.

Stress radiography has been commonly used to evaluate valgus laxity; however, the use of stress ultrasound (SUS) is being increasingly reported.[2,4,10,11,18,20,22,23] Nevertheless, the limb position for SUS has not been standardized. Ciccotti et al[4] evaluated valgus laxity in baseball players in the sitting position with 30° of elbow flexion and 90° of forearm supination and reported that valgus laxity was

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greater on the throwing side. Several reports also applied the same limb position method for SUS.[2,18] On the other hand, Sasaki et al[20] evaluated valgus laxity among baseball players in the supine position, 90° of elbow flexion, and forearm neutral rotation; they reported that valgus laxity was greater on the throwing side. This limb position method for SUS was applied in similar studies.[10,11,22,24] However, it is unclear which limb position method more clearly detects valgus laxity in baseball players.

The purpose of this study was to determine the method that can detect valgus laxity in baseball players (90° or 30° of elbow flexion) and to directly compare the 2 positions to report which elbow position method better represents the increased valgus laxity characteristics of baseball players. We hypothesized that the 90° of flexion method, with an elbow joint flexion angle similar to that of the throwing motion, is superior to the 30° of flexion method.

METHODS

Study Population

Eighteen asymptomatic college baseball players (4 pitchers and 14 fielders) who belonged to a college baseball club between April and November 2021 were included in this study. All participants were young men with no history of elbow pain or elbow surgery. The overall age of the participants was 18 to 20 years (mean ± SD, 18.8 ± 0.5 years), and they had 9 to 12 years (mean ± SD, 10.6 ± 0.9 years) of baseball experience. Seventeen were right-handed throwers and 1 was a left-handed thrower. All participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the ethics committee of our institution.

Assessment

For all participants, the medial elbow joint space (MEJS), defined as the distance between the medial distal end of the humeral trochlea and the proximal end of the ulnar sublime tubercle, was measured on rest days when they had no athletic training. We used an ultrasound system with an 11-MHz linear array transducer (SONIMAGE MX1; Konica Minolta Japan Inc) and a standard transducer gel to capture images at 90° and 30° of elbow flexion, with the elbow at rest and under valgus stress (Figure 1). Valgus laxity was then calculated as the difference between MEJS values under valgus stress and at rest.

The elbow limb positions were based on previous studies.[4,22] In the 90° of flexion position, the participant was positioned supine on the examination table, with 90° of shoulder abduction, 90° of elbow flexion, and neutral forearm rotation. At rest, the forearm was placed on the examination table to avoid valgus stress of the weight of the forearm. If the shoulder joint external rotation was below 90°, a towel was placed under the forearm. Under valgus stress, the position of the participant was adjusted as shown in Figure 1B. Additionally, a handheld dynamometer (μTas F-2; ANIMA Co, Ltd) adjusted to 2.5 kgf of valgus stress was attached to the proximal wrist joint. In the 30° of flexion position, the participant was positioned in the sitting position, with 90° of shoulder abduction, 30° of elbow flexion, and 90° of forearm supination. A processed acrylic plate was used to maintain the 30° of flexion position of the elbow. Under valgus stress, the same handheld dynamometer adjusted to 3.0 kgf of valgus stress was attached to the ulnar head. An assistant supported the upper arm of the participant with a wooden block to ensure that the valgus stress was properly loaded on the elbow (Figure 2). Forearm rotation and amount of valgus stress in the 2 limb positions were based on previous studies.[4,22]

The fiber direction of the UCL was identified, and a probe was placed parallel to it. Ultrasonographic images of the medial epicondyle, UCL, medial surface of the humeral trochlea, and coronoid process of the ulna depicted in the same field of view were used for MEJS measurements (Figure 3). ImageJ Version 1.53t (National Institutes of Health) was used as the image analysis software.

Three orthopaedic surgeons who use ultrasound in their daily practice (R.M., T.O., and Y.H.) participated in the acquisition of the images, and MEJS measurements were performed by a single orthopaedic surgeon with 10 years of experience (R.M.). We evaluated the intraobserver and interobserver reliability of the MEJS and valgus laxity measurements by using the intraclass correlation coefficient (ICC) on a different set of study participants. Intraobserver reliability data were obtained twice by a single orthopaedic surgeon (R.M.) from 10 elbows with a 1-month interval between measurements. Interobserver reliability data were obtained independently by 2 orthopaedic surgeons (R.M. and S.T.) from 10 elbows each. ICC values were interpreted according to the criteria of Landis and Koch[15]: 0.00 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.00, almost perfect.

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Ethical approval for this study was obtained from the University of Tsukuba (reference No. 1517-3).

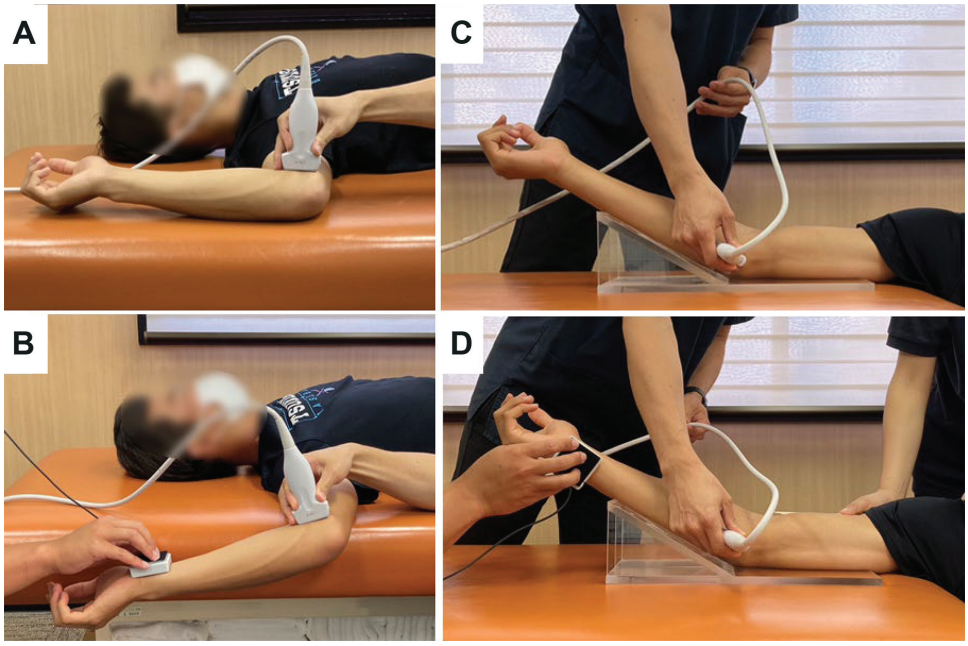

Figure 1. Measurement positions of a study participant: (A) 90° of flexion position with the elbow at rest, (B) 90° of flexion position with the elbow under valgus stress, (C) 30° of flexion position with the elbow at rest, and (D) 30° of flexion position with the elbow under valgus stress.

Figure 2. Photograph showing the 30° of flexion position under valgus stress. An assistant supported the participant's upper arm to ensure that valgus stress was properly loaded on the elbow.

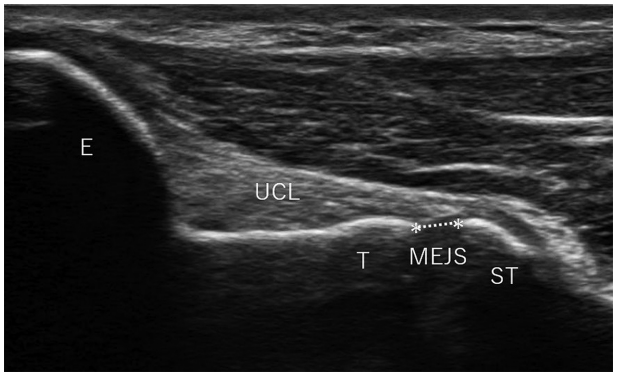

Figure 3. Long-axis image demonstrating the measurement of medial elbow joint space (MEJS; represented by asterisks). E, medial humeral epicondyle; ST, proximal end of the ulnar sublime tubercle; T, medial distal end of the humeral trochlea; UCL, ulnar collateral ligament.

Statistical Analysis

All data were analyzed using SPSS Statistics Version 27 (IBM Corp). First, the normality of each variable was checked using the Shapiro-Wilk test. If the P values of the 2 variables to be compared were $>.05$, they were considered to follow a normal distribution and a paired t test was performed. If either variable had a P value $<.05$, the Wilcoxon signed-rank test was performed. The paired t test or Wilcoxon signed-rank test was performed for comparisons of the measurements between the throwing side and nonthrowing side in both the 30° and 90° of flexion positions. Significant differences were set at a level of 5%. The effect size (ES) was calculated using the Cohen d.

RESULTS

The intraobserver reliability (ICC[1,1]) of the MEJS and valgus laxity measurements ranged from 0.75 to 0.94,

TABLE 1
Intraobserver and Interobserver Reliability of MEJS and Valgus Laxity[a]

	Intraobserver (ICC[1,1])		Interobserver (ICC[2,1])	
	90° of Flexion Position	30° of Flexion Position	90° of Flexion Position	30° of Flexion Position
MEJS				
At rest	0.937	0.75	0.851	0.788
Under valgus stress	0.935	0.872	0.873	0.888
Valgus laxity	0.824	0.843	0.748	0.728

[a]ICC, intraclass correlation coefficient; MEJS, medial elbow joint space.

and the interobserver reliability (ICC[2,1]) ranged from 0.73 to 0.89, indicating substantial to almost perfect agreement for all measurements (Table 1).

Figure 4 shows the MEJS results for each elbow position. At rest, MEJS was 3.9 ± 0.9 mm on the throwing side and 3.8 ± 1.0 mm on the nonthrowing side in the 90° of flexion position. In the 30° of flexion position, it was 4.5 ± 0.8 mm on the throwing side and 4.7 ± 0.7 mm on the nonthrowing side. There was no significant difference between the 2 sides for both limb positions in the resting condition (90° of flexion position: $P = .62$; 30° of flexion position: $P = .56$). Under valgus stress, MEJS was 5.8 ± 1.2 mm on the throwing side and 5.1 ± 1.5 mm on the nonthrowing side in the 90° of flexion position and 5.6 ± 0.7 mm on the throwing side and 5.4 ± 0.7 mm on the nonthrowing side in the 30° of flexion position. In the 90° of flexion position, the MEJS was significantly larger on the throwing side than on the nonthrowing side ($P = .019$; ES = 0.61); whereas in the 30° of flexion position, there was no significant difference between the throwing and nonthrowing sides ($P = .28$).

Valgus laxity was 1.9 ± 0.7 mm on the throwing side and 1.3 ± 0.8 mm on the nonthrowing side in the 90° of flexion position and 1.1 ± 0.7 mm on the throwing side and 0.8 ± 0.6 mm on the nonthrowing side in the 30° of flexion position. In the 90° of flexion position, the difference was significantly larger on the throwing side than on the nonthrowing side ($P = .022$; ES = 0.60), whereas in the 30° of flexion position, there was no difference between the throwing and nonthrowing sides ($P = .13$).

Valgus laxity was significantly larger in the 90° of flexion position than in the 30° of flexion position on the throwing side ($P = .002$; ES = 0.87). Ultrasound images of a representative case are shown in Figure 5. In contrast, there was no significant difference in the valgus laxity between the 30° and 90° of flexion positions on the nonthrowing side ($P = .06$).

DISCUSSION

The major findings from our study were that the elbow valgus laxity on the throwing side was significantly larger (by 0.8 mm) in the 90° of flexion position than in the 30° of flexion position (1.9 vs 1.1 mm; $P = .002$; ES = 0.87), whereas there was no significant difference on the nonthrowing side. Therefore, the valgus laxity of the throwing elbow joint was more clearly detected with a static force in the 90° of flexion position than in the 30° of flexion position among baseball players. This indicates that the 90° of flexion position is the more optimal limb position for SUS evaluation of valgus laxity.

The evaluation of valgus instability at the elbow joint in stress radiography indicated that instability occurs when the medial joint opening exceeds 1 mm.[14] Generally, joint laxity is less severe than joint instability. Considering these factors, a difference of 0.8 mm is a clinically significant value for valgus laxity despite the difference between SUS and stress radiography. Furthermore, the difference between MEJS on the throwing and nonthrowing sides could be detected in the 90° of flexion position but not in the 30° of flexion position. These results lend further support that the 90° of flexion position is the more optimal limb position for the SUS evaluation of valgus laxity.

There are 2 important points regarding this result from a biomechanics perspective. First, the UCL is the primary static stabilizer for valgus stress of the elbow joint.[12,17] Previous research on cadavers indicated that the maximum valgus instability occurs in 90° flexion position when the UCL is dissected.[3] This indicates that the maximum contribution of the UCL as a static stabilizer to valgus stress is in the 90° of flexion position. Morrey and An[16] also reported that in the 90° of flexion position, the contribution of the UCL as a static stabilizer to valgus stress is greater than that of the bone and joints. Second, the maximum valgus stress on the elbow joint in the throwing motion occurs immediately before the maximum external rotation of the shoulder joint and around 90° of elbow flexion.[8] At this instant, the elbow joint is loaded with a large varus torque comparable to the breaking strength of the UCL.[1,8,25] With each pitch, the elbow joint is repeatedly loaded with this stress, resulting in valgus laxity over time.[5,6,8,9,11,13,20] These 2 statements support the hypothesis that the valgus laxity in baseball players is best detected in the 90° of flexion position.

Regarding the difficulty of the procedure in different limb positions, in actual clinical practice, we consider that a reproducible and simple technique such as the 90° of flexion position is visually clear and is considered highly reproducible. In contrast, we consider that the 30° of flexion position is not visually clear and requires time, effort, and measurement with an angle meter to ensure

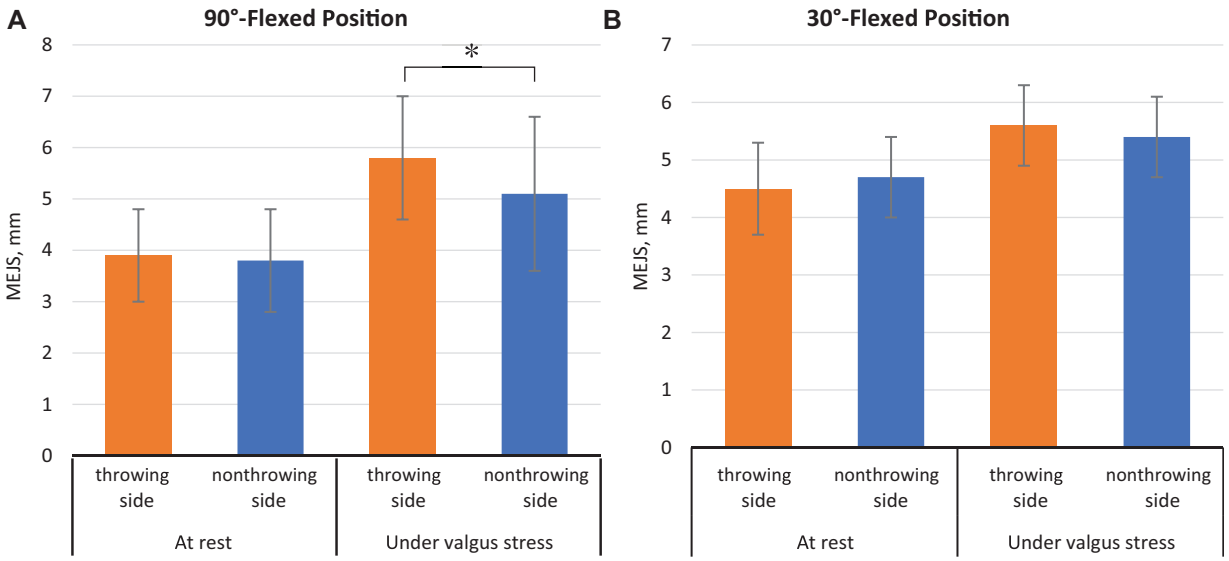

Figure 4. Bar graph illustrating the MEJS for the (A) 90° of flexion position and (B) 30° of flexion position. Error bars indicate standard deviation. *Statistically significant difference between throwing and nonthrowing sides ($P < .05$). MEJS, medial elbow joint space.

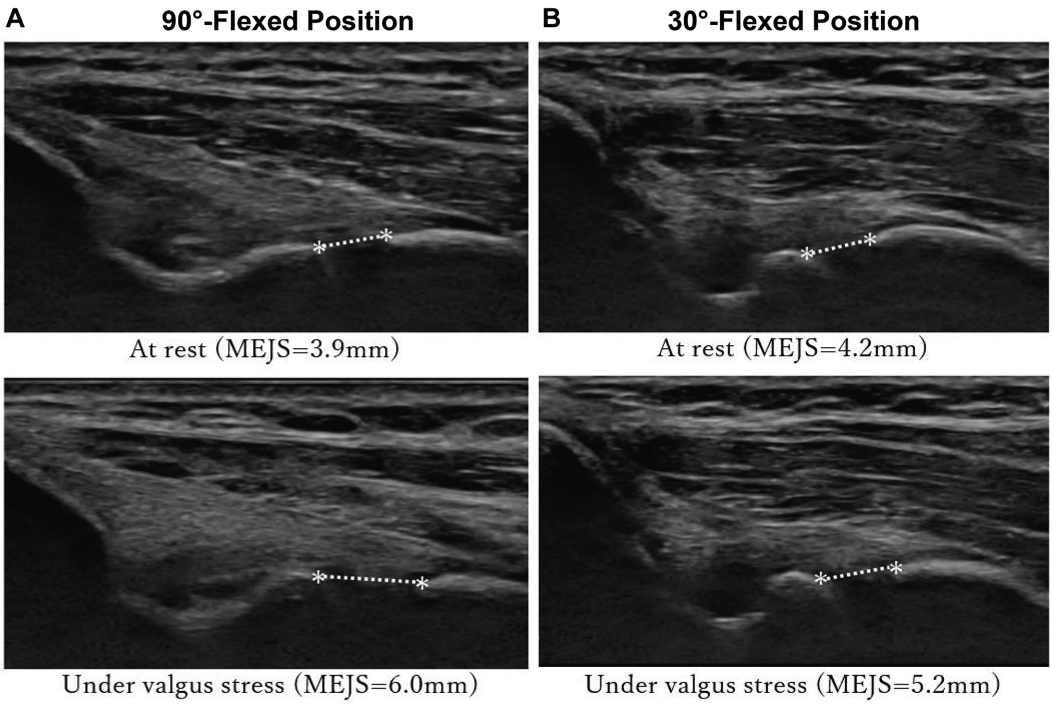

Figure 5. Ultrasound images from a 19-year-old pitcher showing the medial elbow joint space (MEJS; represented by asterisks) on the throwing side for the (A) 90° of flexion and (B) 30° of flexion positions. Valgus laxity was greater at the 90° of flexion position than at the 30° of flexion position (2.1 vs 1.0 mm).

reproducibility. In terms of simplicity, the 90° of flexion position does not require any special equipment. However, in the 30° of flexion position, equipment is needed to properly load valgus stress while maintaining the flexion angle. In this study, a simply processed acrylic plate was used to maintain the 30° of flexion position, but multiple assistants were required to maintain the limb position, such as upper arm support when loading valgus stress. Some studies have indicated using dedicated devices; however, they are expensive and not practical in clinical or sports fields.[2,4,6,10,21,23] We consider that the same can be stated for limb positions other than 30°, such as 45° and 60°.

Therefore, the evaluation method using the 90° of flexion position is easier to use clinically than the evaluation method using the 30° of flexion position.

In this study, the difference between the 2 limb positions is the forearm rotation in addition to the elbow flexion angle. In the 90° of flexion position, the forearm was in neutral rotation, and in the 30° of flexion position, the forearm was in supination. Safran et al[19] investigated the effect of forearm rotation on elbow valgus laxity at 30°, 50°, and 70° of elbow flexion in a cadaveric study. Results showed that when the UCL was intact, valgus laxity was greater in the neutral forearm position compared with forearm pronation or supination at all elbow flexion angles. In this study, forearm rotation in the 30° of flexion position was defined as supination on the basis of previous studies, but it is unclear whether the forearm rotation affected the magnitude of valgus laxity.

Strengths and Limitations

The strengths of this study include the uniformity of the technique, the precision of high-resolution ultrasonography, and the methods being conducted by experienced orthopaedic surgeons. It is possible that previous studies conducted with the 30° of flexion elbow position adopted in this study have not adequately assessed the valgus laxity characteristics of baseball players.

There are several limitations of this study. First, the study is limited to college baseball players. It is not known whether the same results could be obtained for other age or sex groups. Second, the number of participants in this study is small. Third, subgroup analyses by age and years of baseball experience could not be performed because of the small individual differences in these parameters in the participants. Fourth, it did not consider the differences in valgus laxity by forearm rotation within the same elbow flexion angle. Fifth, the 30° of flexion position was not measured under conditions where gravity was applied to the forearm, and this approach may have resulted in differences from the measurements in the 90° of flexion position. Sixth, ultrasound effectiveness depends on the observer. Although intraobserver and interobserver reliability was high in this study, results can differ depending on the observer's experience with SUS. Seventh, this study did not investigate the association between valgus laxity and injuries, such as UCL injuries.

CONCLUSION

In the current study, the 90° of flexion position of the elbow more clearly detected valgus laxity than the 30° of flexion position, indicating that the 90° of flexion position is more optimal for SUS evaluation of elbow valgus laxity in baseball players.

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Original Article

Proton Pump Inhibitors and Cyclin-Dependent Kinase 4/6 Inhibitors in Patients With Breast Cancer

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Abstract

Background: Proton pump inhibitors (PPIs) reduce the bioavailability of several anticancer drugs. The impact of PPIs co-administered with cyclin-dependent kinase 4 and 6 inhibitors is controversial. We aimed to clarify whether the concomitant use of PPIs impacts palbociclib and abemaciclib effectiveness in breast cancer treatment.

Patients and Methods: This multicenter, retrospective, observational study, conducted across 4 medical institutions in Japan, consecutively included patients with endocrine-resistant metastatic breast cancer, receiving palbociclib or abemaciclib between December 2017 and August 2022. Propensity score-matched analyses were performed. Treatment efficacy and safety with and without PPIs were compared. Progression-free survival and overall survival were estimated using the Kaplan-Meier method and compared using a log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio.

Results: The study included 240 patients. After 1:1 matching, 112 patients were treated with and without PPIs. The median progression-free survival period was 1.2 years in the PPI group and 1.3 years in the non-PPI group (hazard ratio, 1.19; 95% CI, 0.70-2.02). The median overall survival period was 3.6 years in the PPI group, whereas it was not reached in the non-PPI group (hazard ratio, 1.23; 95% CI, 0.61-2.47). Consistent results were obtained for subgroups receiving palbociclib (n = 177) and abemaciclib (n = 63) without propensity score matching. Adverse event incidence and severity were similar in both groups.

Conclusion: The effectiveness of cyclin-dependent kinase 4/6 inhibitors is unlikely to be affected by concomitant PPI use. Future prospective pharmacokinetic studies are warranted.

Key words: breast cancer; palbociclib; abemaciclib; proton pump inhibitor; propensity score.

Implications for Practice

The impact of the co-administration of proton pump inhibitors (PPIs) with cyclin-dependent kinase 4 and 6 inhibitors is controversial. This study clarified whether the concomitant use of PPIs impacts the effectiveness of palbociclib and abemaciclib in patients with endocrine-resistant metastatic breast cancer using real-world data. Importantly, we identified that progression-free survival and overall survival were unaffected by the concomitant use of PPIs. The findings of this study suggest that further consideration should be given to changing the prescription of PPIs for patients receiving palbociclib or abemaciclib.

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Introduction

Breast cancer (BC), the most common cancer and the fourth leading cause of cancer-related death in women, affected approximately 2.3 million individuals worldwide in 2020.[1] Japan reported approximately 97,000 cases of BC in 2019.[2] Approximately one in 9 Japanese women are estimated to develop BC. Unfortunately, all patients with metastatic BC (mBC) are incurable. Approximately 60% of mBC cases are luminal, hormone receptor-positive, and human epidermal growth factor receptor type 2 (HER2) negative.[3]

Compared with traditional endocrine monotherapy, combination therapy with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors, consisting of palbociclib, ribociclib, and abemaciclib, and endocrine therapy, such as aromatase inhibitors or antiestrogen, has remarkably prolonged progression-free survival (PFS) in patients with hormone receptor-positive and HER2-negative mBC.[4-9] The use of CDK4/6 inhibitors plus endocrine therapy is recommended as the new standard of care for first- or second-line treatment of pre- and postmenopausal patients with hormone receptor-positive and HER2-negative mBC.[10,11] Notably, CDK4/6 inhibitors have a different mechanism of action than other cancer chemotherapies. They prevent cellular DNA synthesis by inhibiting cell progression from the G1 to S phase, thereby suppressing cancer cell proliferation.[12] In Japan, oral palbociclib and abemaciclib are newly approved for hormone receptor-positive and HER2-negative mBC treatment. However, ribociclib has not been approved; a reason for this is the high toxicity profile, including abnormal hepatic function in the Japanese population.[13]

The concomitant use of proton pump inhibitors (PPIs) substantially decreases PFS in patients with mBC treated with palbociclib and ribociclib.[14-16] The potential mechanism of these drug-drug interactions (DDIs) may include gastric pH elevation by PPIs. PPIs reduce the bioavailability of several anticancer drugs through dissolution and absorption.[17-20] Conversely, several studies do not support the existence of the DDIs.[21-24] Therefore, the impact of co-administration of PPIs with CDK4/6 inhibitors remains controversial. These previous studies shared a retrospective, observational design and included patients with hormone receptor-positive and HER2-negative mBC. However, in several of those studies, treatment lines and the corresponding patient eligibility criteria were not specified and the sensitivity to endocrine therapy of the patients were not considered. The PFS of endocrine-sensitive patients receiving palbociclib was reportedly 24.8 months, whereas that in endocrine-resistant patients was only 9.5 months.[4,5] As these different results cannot be equally evaluated, in the present study, we pursued in patients with endocrine resistance who had never undergone chemotherapy, because we thought that the overall survival (OS) of endocrine-sensitive patients treated with CDK4/6 inhibitors is influenced by second-line or subsequent therapy and that a 5-year follow-up may be too short since endocrine-sensitive patients have a relatively favorable prognosis. To the best of our knowledge, the potential DDIs mentioned above have not yet been investigated in the Japanese population, and no studies are available on the DDIs between PPIs and abemaciclib. Thus, we hypothesized that concomitant PPI use decreases the effectiveness of CDK4/6 inhibitors. The present study aimed to clarify, using real-world data, whether concomitant PPI use alters the effectiveness of palbociclib and abemaciclib in patients with hormone receptor-positive and HER2-negative mBC.

Patients and Methods

Study Design

This multicenter, retrospective, observational, case-control study was conducted across 4 medical institutions: National Cancer Center Hospital East (Chiba, Japan), Keio University Hospital (Tokyo, Japan), Miyagi Cancer Center (Miyagi, Japan), and Gifu University Hospital (Gifu, Japan). Patient data were obtained from the medical records of each institution. Data integration and subsequent analyses were performed at the Keio University Faculty of Pharmacy (Tokyo, Japan). The methodology adopted herein adhered to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[25]

The eligibility criteria for the patients were as follows: (1) aged ≥ 18 years and consecutively presenting with a diagnosis of hormone receptor-positive and HER2-negative mBC (hormone receptor-positive was defined as tumors with estrogen and/or progesterone receptor expression > 1%; HER2-negative was defined as a score of 0, 1+, or 2 + using immunohistochemistry; and negative result as per in situ hybridization[11]); (2) received palbociclib (125 mg taken orally once daily for 21 consecutive days followed by 7 days off in 28-day cycles) or abemaciclib (150 mg taken orally twice daily) plus endocrine therapy for the first time between December 2017 and August 2022; (3) underwent second-line or subsequent-line endocrine therapy (for patients who have de novo metastatic cancer or experienced progression during neoadjuvant chemotherapy prior to surgery); (4) underwent first-line or subsequent-line endocrine therapy (for patients who experienced progression during treatment or within 12 months of completion of adjuvant endocrine therapy, and (5) underwent second-line or subsequent-line endocrine therapy (for patients who developed recurrent disease > 12 months of completing that treatment). These definitions of first- and second-line endocrine therapies were based on the American Society of Clinical Oncology guidelines 2016.[26] The dose reduction of CDK4/6 inhibitors and clinical follow-up were modified at the clinician's discretion according to the efficacy and/or safety profile of each patient.

The exclusion criteria were as follows: (1) refusal to use medical records for research; (2) insufficient or missing data; and (3) history of chemotherapy for disease control of mBC prior to treatment with CDK4/6 inhibitors, except for neoadjuvant or adjuvant chemotherapy.

Data Collection

Data of patients were de-identified and managed anonymously. Collected data included age, sex, menopausal status, Eastern Cooperative Oncology Group performance status (ECOG PS), metastatic site, number of metastatic sites, medical history (including CDK4/6 inhibitor and PPI use), treatment line, date of progression and/or death at the time of initiation of CDK4/6 inhibitors, and the incidence of adverse events of grade ≥ 3 while taking CDK4/6 inhibitors or up to 3 months after taking. The date of progression was defined as the first incidence of disease progression based on computed tomography using the Response Evaluation Criteria in Solid Tumours criteria version 1.1[27] or clinical progression. Adverse events were graded according to the Common Terminology

Criteria for Adverse Events version 5.0.[28] Each attending physician advised against the intake of strong inhibitors or inducers of cytochrome P450 3A4 based on their knowledge. Treatment groups were defined as "concomitant use of PPIs" if PPI administration covered the entire or more than half of the treatment period with palbociclib[15,24] or "no concomitant use of PPIs" if PPI administration covered less than half of the treatment period. Moreover, "visceral" refers to lung, liver, brain, pleural, and peritoneal involvement. The follow-up period ended on November 30, 2022.

Endpoints

The efficacy endpoints were PFS and OS when treated with or without PPIs. The safety endpoint was adverse events when treated with or without PPIs. PFS was defined as the period from the date of initiation of CDK4/6 inhibitors to the date of disease progression or death from any cause, whereas OS was defined as the period from the date of initiation of CDK4/6 inhibitors to the date of death from any cause. Patients without documented progressive disease or those who were still alive were censored for PFS and OS, respectively, on the date of the last follow-up.

Statistical Analysis

Baseline patient characteristics are reported as median (interquartile range) for continuous variables and proportions for categorical variables. PFS and OS were estimated using the Kaplan-Meier method and compared using a log-rank test. Propensity score-matched analysis was performed to minimize potential selection bias due to lack of randomization.[29] Propensity scores of concomitant PPI use were estimated using a logistic regression model based on the following clinically selected covariates: age, ECOG PS (0-1 *vs.* 2), disease site (visceral *vs.* non-visceral), number of metastases, and previous lines of endocrine treatment (1 *vs.* ≥ 2). In a sensitivity analysis, two propensity score-adjusted analyses were performed: (1) a multivariable Cox proportional hazards model including the propensity score of concomitant use of PPIs as a covariate and (2) the inverse probability of treatment weighting (IPTW) method.[30] The results are presented as hazard ratios (HR) and 95% CIs. As a post hoc analysis, the Bayesian posterior probability of HRs from 0.83 to 1.2 based on non-informative prior distribution was computed to assess the equivalence.[31] The follow-up time was calculated using the reverse Kaplan-Meier estimate.[32] All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS Statistics version 29 (IBM, Armonk, NY, USA). All *P*-values were 2 sided, and the significance level was set at 0.05.

Ethics Statement

The study protocol was representatively approved by the Ethics Committees of the Keio University School of Medicine (approval number: 20221136). Permission to conduct the present study was then obtained from each facility. This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour, and Welfare of Japan. The requirement for written informed consent was waived by the ethics review committees owing to the retrospective nature of this study. Accordingly, we provided patients with an opt-out method through the official website of each hospital.

Results

Patient Characteristics

Figure 1 shows the patient enrollment flowchart. Overall, 596 patients were initially surveyed at the 4 sites, and 240 met the eligibility criteria. Among them, 58 patients were taking CDK4/6 inhibitors with PPIs. Propensity score-matched analysis resulted in 112 patients, who were divided into groups treated with (PPI group; $n = 56$) and without (non-PPI group; $n = 56$) PPIs. After matching, the distributions of the propensity score in both groups were similar (Supplementary Fig. S1). Table 1 presents the baseline patient characteristics. The median age of the patients was 71 (interquartile range, 61-75) years. Of the 78 patients who were receiving palbociclib, 58 and 20 were taking it as capsules and tablets, respectively. Approximately 70% of patients used CDK4/6 inhibitors in the first- or second-line endocrine therapy. The number of metastases was within 5, and more than half of the patients had visceral metastases.

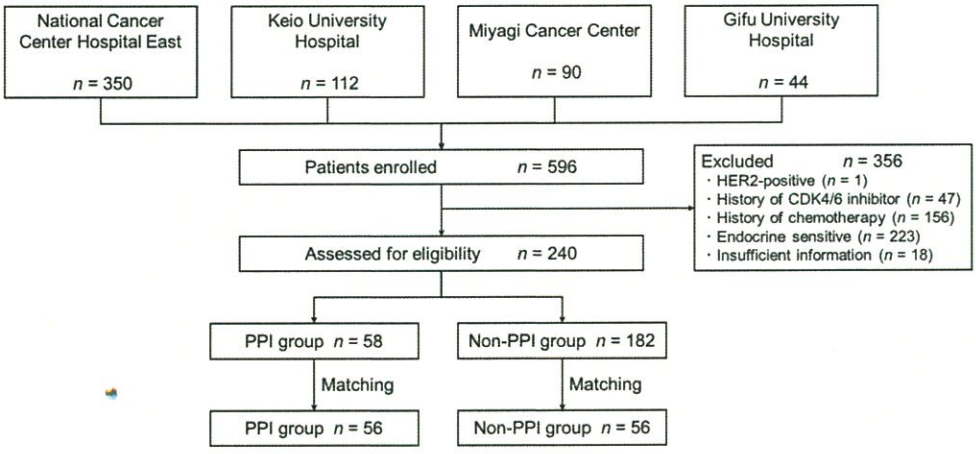

Figure 1. Patient enrollment flowchart. Abbreviations: HER2, human epidermal growth factor receptor type 2; CDK4/6, cyclin-dependent kinases 4 and 6; PPI, proton pump inhibitor.

Table 1. Patient characteristics.

Characteristics	Unmatched patients (n = 240)		Matched patients (n = 112)	
	PPI (n = 58)	Non-PPI (n = 182)	PPI (n = 56)	Non-PPI (n = 56)
Age (years), median (IQR)[a]	71 (60-75)	62 (50-70)	71 (60-75)	70 (62-75)
Sex				
Female	57 (98)	180 (99)	55 (98)	55 (98)
Male	1 (2)	2 (1)	1 (2)	1 (2)
Menopause				
Premenopause	8 (14)	47 (26)	8 (14)	4 (7)
Postmenopause (or male sex)	50 (86)	135 (74)	48 (86)	52 (93)
ECOG PS[a]				
0-1	52 (90)	178 (98)	52 (93)	53 (95)
2	6 (10)	4 (2)	4 (7)	3 (5)
Treatment line[a]				
1st	16 (28)	70 (39)	16 (29)	15 (27)
2nd	25 (43)	70 (39)	23 (41)	26 (46)
≥ 3rd	17 (29)	42 (23)	17 (30)	15 (27)
Number of metastases, median (IQR)[a]	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Metastatic site[a]				
Visceral	36 (62)	107 (59)	34 (61)	36 (64)
Non-visceral	22 (38)	75 (41)	22 (39)	20 (36)
CDK4/6 inhibitor				
Palbociclib capsule	34 (59)	91 (50)	33 (59)	25 (45)
Palbociclib tablet	11 (19)	41 (23)	10 (18)	10 (18)
Abemaciclib	13 (22)	50 (28)	13 (23)	21 (38)
Dose reduction of CDK4/6 inhibitor				
Yes	36 (62)	125 (69)	36 (64)	40 (71)
No	22 (38)	57 (31)	20 (36)	16 (29)
Concomitant endocrine therapy				
Anastrozole	2 (3)	19 (10)	2 (4)	7 (13)
Letrozole	15 (26)	34 (19)	15 (27)	11 (20)
Exemestane	1 (2)	4 (2)	0	2 (4)
Tamoxifen	0	1 (1)	0	1 (2)
Fulvestrant	40 (69)	124 (68)	39 (70)	35 (63)
Concomitant LH–RH agonist				
None	51 (88)	139 (76)	49 (88)	53 (95)
Leuprorelin acetate	5 (9)	35 (19)	5 (9)	3 (5)
Goserelin acetate	2 (3)	8 (4)	2 (4)	0
PPI used				
Omeprazole	3 (5)		3 (5)	
Lansoprazole	27 (47)		25 (45)	
Rabeprazole	8 (14)		8 (14)	
Esomeprazole	10 (17)		10 (18)	
Vonoprazan	10 (17)		10 (18)	

Abbreviations: IQR, interquartile range; PPI, proton pump inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; CDK4/6 inhibitor, cyclin-dependent kinases 4 and 6; LH–RH, luteinizing hormone-releasing hormone.
Data are presented as the number (%) of patients unless otherwise indicated. Percentages have been rounded and may not total 100.
[a]Age, ECOG PS, treatment line, number of metastases, and metastatic sites were used to match the two groups.

Approximately two-thirds of the patients in both groups required dose reduction of CDK4/6 inhibitors, and no significant difference in dosage between the two groups was noted. In total, 66% of the concomitant endocrine therapy included fulvestrant use. Lansoprazole was the most commonly prescribed PPI (45%).

Efficacy

The median follow-up time was 2.6 (95% CI, 2.2-3.1) years. The median PFS was 1.2 (95% CI, 0.7-1.7) and 1.3 (95% CI, 1.1-2.5) years in the PPI and non-PPI groups, respectively (log-rank test: P = 0.53; Fig. 2). The crude HR was 1.19 (95%

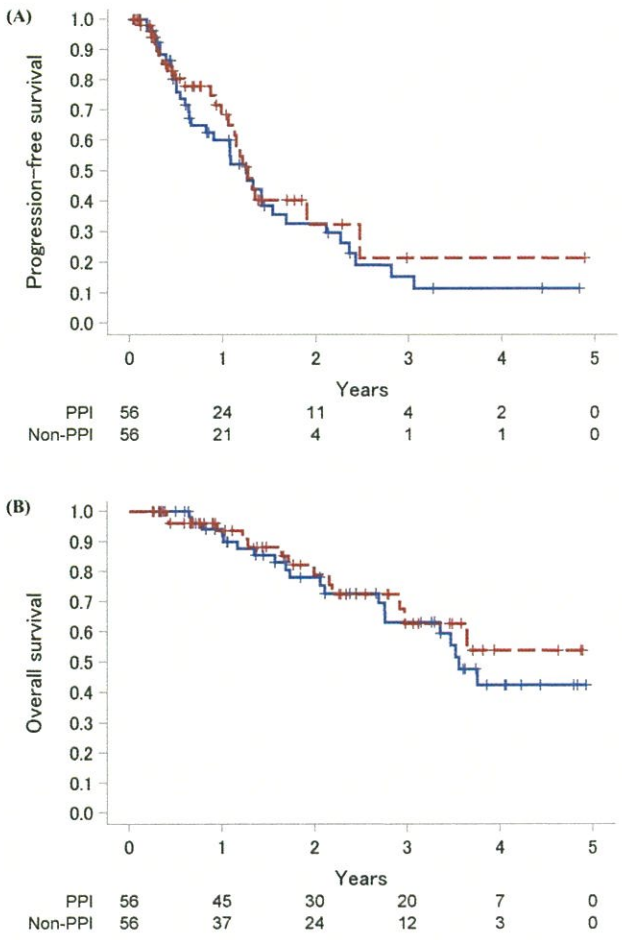

Figure 2. Kaplan-Meier survival curves according to concomitant or non-concomitant PPI use. Kaplan-Meier survival curves were constructed according to the use of PPIs in the propensity score-matched patients. Solid and dashed lines represent the PPI and non-PPI groups, respectively. The number of patients at risk are shown at the bottom. (A) Progression-free survival. (B) Overall survival. Abbreviation: PPI, proton pump inhibitor.

CI, 0.70-2.02) according to the univariable analysis. The median OS period was 3.6 (95% CI, 2.8-not reached) years in the PPI group, whereas it was not reached in the non-PPI group (log-rank test: $P = 0.57$). The crude HR was 1.23 (95% CI, 0.61-2.47) according to the univariable analysis.

Sensitivity analyses using a propensity score-adjusted model and IPTW analysis for PFS revealed consistent results (HR, 1.11; 95% CI, 0.73-1.68; $P = 0.63$ and HR, 1.09; 95% CI, 0.76-1.57; $P = 0.62$, respectively). Similar results were obtained for OS using propensity score-adjusted and IPTW analyses (HR, 1.21; 95% CI, 0.68-2.15; $P = 0.51$ and HR, 1.26; 95% CI, 0.71-2.24; $P = 0.43$, respectively). The Bayesian posterior probability of HRs for the PFS from 0.83 to 1.2 ranged from 42% to 77% (Table 2).

Subgroup analyses were performed separately for palbociclib ($n = 177$) and abemaciclib ($n = 63$) without propensity score matching. The median PFS in the palbociclib group was 1.3 (95% CI, 0.6-2.3) and 1.1 (95% CI, 0.9-1.3) years in the PPI and non-PPI groups, respectively (Supplementary Fig. S2), with no significant difference (HR, 0.94; 95% CI, 0.61-1.46; $P = 0.80$). Similarly, OS did not differ significantly (HR, 1.47; 95% CI, 0.82-2.62; $P = 0.19$).

Similar results were observed for abemaciclib (PFS: HR, 1.30; 95% CI, 0.53-3.17; $P = 0.56$ and OS: HR, 1.22; 95% CI, 0.33-4.47; $P = 0.76$) (Supplementary Fig. S3).

Additionally, 125 and 52 patients were classified into the palbociclib capsule and tablet groups, respectively. The analysis indicated no significant differences in either PFS or OS for the capsule (PFS: HR, 1.06; 95% CI, 0.66-1.71; $P = 0.80$ and OS: HR, 1.40; 95% CI, 0.76-2.58; $P = 0.28$) (Supplementary Fig. S4). Similar results were obtained for the tablets (data not shown).

Safety

Table 3 presents grade 3/4 adverse events in the matched population. The proportion of adverse events was similar for each CDK4/6 inhibitor, regardless of PPI use. Palbociclib was associated with a high incidence of neutrophil count decreased, whereas abemaciclib was associated with a high incidence of diarrhea. The PPI and non-PPI groups did not differ significantly (Fisher's exact tests: $P = 0.75$ and $P = 1.00$, respectively). No grade 5 adverse events were observed.

Discussion

No study to date has focused on the association between concomitant PPI use and the effectiveness of CDK4/6 inhibitors in patients with endocrine resistance who have never undergone chemotherapy. In the present study, we found that concomitant PPI use did not significantly reduce PFS and OS in propensity score-matched patients. Additionally, the sensitivity and subgroup analyses showed consistent results. To the best of our knowledge, this is the first multicenter study examining the effect of PPIs co-administered with CDK4/6 inhibitors on survival outcomes in Japanese patients with endocrine resistance in a real-world setting.

The study population was relatively homogeneous, with a large number of survival events (i.e., PFS and OS). We focused on patients resistant to endocrine therapy who had never undergone chemotherapy. This was determined with reference to eligible patients in the PALOMA-3 phase III trial.[5] We considered this population suitable for clarifying whether concomitant PPI use alters the effectiveness of palbociclib and abemaciclib; the efficacy did not differ significantly between the groups treated with and without PPIs in the sensitivity and subgroup analyses. These results did not support our hypothesis that concomitant PPI use decreases the effectiveness of CDK4/6 inhibitors. Sun et al[33] stated the pharmacokinetics of palbociclib capsules with PPIs. Under fasting conditions, co-administration of PPIs and palbociclib capsules decreased the palbociclib mean area under the concentration-time curve from time 0 to infinity by 62%; however, under fed conditions, it decreased by only 13%. If patients take palbociclib capsules appropriately after meals, the effect of PPIs on palbociclib blood levels may not be clinically significant. The differences between these DDI studies may be attributed to differences in the healthcare systems for outpatients among countries. The present study was conducted at university hospitals with more than 600 beds and designated cancer centers in Japan, wherein patients are managed by high-level experts in cancer treatment. Particularly, at the National Cancer Center Hospital East, patients received individual guidance from hospital pharmacists regarding oral anticancer drugs. Patient education is essential for developing adherence. In Japan, hospital pharmacists provide patients with adequate education

Table 2. HRs of PFS, OS, and the Bayesian posterior probability of HRs from 0.83 to 1.2.

	HR (95% CI)	*P*-value	Posterior probability (%)
PFS			
Propensity score matching	1.19 (0.70-2.02)	0.53	42
Multivariable analysis	1.11 (0.73-1.68)	0.63	57
IPTW	1.09 (0.76-1.57)	0.62	77
OS			
Propensity score matching	1.23 (0.61-2.47)	0.57	34
Multivariable analysis	1.21 (0.68-2.15)	0.51	39
IPTW	1.26 (0.71-2.24)	0.43	38

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; IPTW, inverse probability of treatment weighting.

Table 3. Grade 3/4 adverse events.

	Palbociclib ($n = 78$)		Abemaciclib ($n = 34$)	
	PPI ($n = 43$)	Non-PPI ($n = 35$)	PPI ($n = 13$)	Non-PPI ($n = 21$)
Hematological toxicity				
Neutrophil count decreased	36 (84)	31 (89)	7 (54)	4 (19)
White blood cell count decreased	20 (47)	11 (31)	2 (15)	0
Anemia	5 (11)	3 (9)	1 (8)	3 (14)
Platelet count decreased	4 (9)	1 (3)	0	0
Febrile neutropenia	0	0	1 (8)	0
Non-hematological toxicity				
Diarrhea	1 (2)	0	3 (23)	4 (19)
Pneumonitis	3 (7)	2 (6)	0	2 (10)
AST level increased	0	2 (6)	1 (8)	2 (10)
ALT level increased	0	1 (3)	1 (8)	2 (10)
Stevens–Johnson syndrome	0	0	1 (8)	0
Skin ulceration	1 (2)	0	0	0
Malaise	0	1 (3)	0	0
Skin infection	0	1 (3)	0	0
Appendicitis	0	1 (3)	0	0
Nausea	0	0	0	1 (5)
Anorexia	0	0	1 (8)	0

Abbreviations: PPI, proton pump inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Data are presented as the number (%) of patients.

and follow-up on medications.[34] Moreover, the most important feature of the Japanese healthcare system is the separation of prescription and dispensary; community pharmacies provide thoughtful guidance to outpatients regarding oral anticancer drugs.[35] Therefore, we consider that our patients sufficiently well-educated to take the palbociclib capsule after meals according to the package insert of the capsule. We believe that these factors are associated with the effectiveness of CDK4/6 inhibitors in patients treated with PPIs. This hypothesis is supported by the finding that dose reduction of CDK4/6 inhibitors was independent of concomitant PPI use. Assuming PPIs reduce the blood concentration of CDK4/6 inhibitors, more patients in the non-PPI group than in the PPI group should have required dose reduction of CDK4/6 inhibitors. Notably, the safety was similar between the two groups. We posited that if concomitant PPI use was to reduce the blood concentration of CDK4/6 inhibitors, the incidence and severity of adverse events should decrease; however, this trend was not observed. This result can be explained in the same manner as the efficacy results.

To date, no pharmacokinetic data on DDIs between abemaciclib and PPIs have been reported. The abemaciclib tablet formulation is weakly basic, and its solubility is expected to be pH-dependent. Abemaciclib has structural characteristics similar to those of palbociclib, potentially explaining the consistent results. To the best of our knowledge, this is the first study to demonstrate the DDIs between abemaciclib and PPIs. Abemaciclib is approved for mBC, and as an adjuvant therapy, it can be used in more patients than palbociclib,[8,9,36] highlighting the potential clinical significance of our findings.

Concomitant PPI use reportedly reduces the effectiveness of CDK4/6 inhibitors.[14-16] Our study is consistent with these

previous reports in sharing a retrospective, observational design for patients with hormone receptor-positive and HER2-negative mBC. However, there are some contrasting findings.[21-24] In contrast to our results, Lee et al[16] reported DDIs between palbociclib capsules and PPIs in 1,310 patients and concluded, using propensity score matching, that concomitant PPI use significantly reduced the effectiveness of palbociclib capsules. The authors attributed this result to the decreased solubility of palbociclib capsules. However, ECOG PS and exact PFS were not evaluated because they used insurance claims data. Therefore, the time to the next treatment was alternatively used for PFS. However, this evaluation method is inaccurate. In the present study, both palbociclib capsules (to be taken after meals) and tablets (can be taken regardless of meals) were included, with no reduced efficacy observed. Given the reformulation of palbociclib from capsules to tablets, DDIs between palbociclib tablets and PPIs are unlikely to remain clinically relevant.

This study has various strengths. First, it included patients from 4 medical institutions across Japan. Therefore, our data may be applicable to similar populations in clinical settings and will presumably play a crucial role in shared decision-making between patients and a multidisciplinary care team comprising doctors, pharmacists, and nurses. In particular, we believe that this study provides valuable evidence for their decision to first-line endocrine therapy for patients who experienced progression during treatment or within 12 months of completion of adjuvant endocrine therapy. Second, we focused on patients with endocrine-resistant mBC who had never undergone chemotherapy. Third, the follow-up period was relatively long. We evaluated both the PFS and OS. Finally, we performed propensity score matching, resulting in both groups being well-balanced. This analysis increases the robustness of the results and is a novel feature of our study.

Limitations

Our study has some limitations. First, this was a retrospective, observational, case-control study; therefore, information bias exists. Second, the cohort size was small; therefore, we could not include any additional factors for propensity score matching and were unable to match the types of CDK4/6 inhibitors. Third, no exact data on adherence to CDK4/6 inhibitors or PPIs were obtained; we used prescription history. Additionally, we were unable to perform quantitative or qualitative assessments to establish the patterns of drug timing. Fourth, this study was a discovery cohort. Therefore, our findings need to be validated in future studies. Fifth, no pharmacokinetic data for the CDK4/6 inhibitors were obtained. Therefore, prospective pharmacokinetic studies should be conducted. Finally, the current standard treatment is the use of CDK4/6 inhibitors and endocrine therapy drugs as first-line treatments for patients with hormone receptor-positive and HER2-negative mBC. Therefore, studies in patients with endocrine sensitivity would be more applicable to current practice than studies in endocrine-resistant populations. We aim to evaluate the outcomes for patients in the first-line setting treated with CDK4/6 inhibitors and endocrine therapy drugs in future investigations.

Conclusions

This study suggests that the effectiveness of CDK4/6 inhibitors is unlikely to be affected by concomitant PPI use in Japanese patients with hormone receptor-positive and HER2-negative endocrine-resistant mBC. Further consideration should be given to changing the prescription of PPIs for patients taking palbociclib or abemaciclib. Our findings may also be generalizable to Japanese patients, warranting future prospective pharmacokinetic studies.

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Conflict of Interest

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Author Contributions

Conception/design: H.K., T.N. Provision of study material or patients: T.M., T.H., Y.K., A.N., S.K., Y.A.-N., T.S., K.O., A.S., F.O., M.F. Collection and/or assembly of data: K.T., M.I., H.I., M.T., M.K., H.K. Data analysis and interpretation: K.T., R.U., H.K. Manuscript writing: K.T., H.K. Final approval of manuscript: All authors.

Data Availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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Clinical Research

Is a Novel Fluoroscopic Intraoperative Reference System Superior to Conventional Management for Distal Radius Fracture Reduction? A Propensity-matched Comparative Study

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Abstract

Background Preoperative planning is generally performed to simulate the process of reduction as well as to determine the size and placement of implants in patients undergoing distal radius fracture surgery. We previously described a three-dimensional (3D) digital preoperative planning system for the osteosynthesis of distal radius fractures, and we have developed a novel intraoperative referencing system that superimposes preoperative planning (such as plate position and length) onto fluoroscopic images during surgery; however, its efficacy has not been evaluated compared with conventional planning and surgery.

Questions/purposes Does use of a novel intraoperative referencing system result in (1) better Mayo wrist scores at 3 and 6 months after surgery and (2) less loss of reduction in terms of ulnar variance, palmar tilt, and radial inclination on plain radiographs taken 1 week, 3 months, and 6 months after surgery compared with conventional preoperative planning?

Methods Between April 2014 and October 2021, we treated 294 patients with open reduction and volar plate fixation for distal radius fractures. Of 294 patients, 65% (191) underwent surgery using either conventional preoperative planning or a novel intraoperative referencing system. The remaining patients were excluded because they were younger than 18 years, they had some missing medical records related to the clinical outcomes, or they had a previous history of upper extremity injuries. During that time, we generally treated fractures with volar plates when there was: more than 2 mm of stepoff/gap in the articular surface, a dorsal tilt more than 15°, radial inclination less than 15°, or radial shortening more than 5 mm. Generally, we used a flexor carpi radialis approach. In some patients who had dorsal fragments, we added a dorsal approach. At that time, we were developing the new

Each author certifies that there are no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article related to the author or any immediate family members.
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Clinical Orthopaedics and Related Research® neither advocates nor endorses the use of any treatment, drug, or device. Readers are encouraged to always seek additional information, including FDA approval status, of any drug or device before clinical use.
Ethical approval for this study was obtained from our institutional review board, registered as T2019-0178 and T2022-0041.
The work was performed at the Department of Orthopaedic Surgery, Tokyo Medical University Ibaraki Medical Center, Ami, Japan.

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intraoperative referencing system, so it was not used consistently. To arrive at a fair assessment, we opted to perform propensity matching based on age, gender, and AO fracture type. During the period in question, 36% (69 of 191) of patients with distal radius fractures who received a volar plate were treated using our novel intraoperative referencing system, and 64% (122 of 191) had surgery using conventional preoperative planning (control group). Of those, 91% (63 of 69) of patients who were treated with the intraoperative referencing system and 89% (108 of 122) of those in the control group were available for follow-up with all imaging and Mayo wrist scores at least 6 months after surgery. After propensity matching, that left us with two groups of 39 patients, who were well matched in terms of age and fracture type; these were the study groups. We also tried to match them according to gender, but there were fewer patients in the intraoperative referencing group, and the percentage of women for each group differed: 70% (44 of 63) in the intraoperative referencing group and 76% (82 of 108) in the control group. Also, there were fewer men with C3 fractures in the control group. Therefore, 64% (25 of 39) of patients in the intraoperative referencing group were women and 77% (30 of 39) of patients in the control group were women. In the intraoperative referencing group, our novel intraoperative referencing system was used in combination with the 3D digital preoperative planning system for preoperative planning. In the control group, preoperative planning was performed manually in a conventional manner using tracing paper and implant templates or using a digital template. We compared the groups in terms of operative duration, the radiation dose used in surgery, and Mayo wrist scores at 3 and 6 months after surgery. We also compared the groups in terms of loss of reduction on ulnar variance, palmar tilt, and radial inclination on plain radiographs taken 3 months and 6 months after surgery. We considered the plain radiograph taken 1 week after surgery as a baseline. Each item was compared between the image fusion and control groups using a Welch t-test.

Results Mayo wrist scores were no different between the intraoperative referencing system and the control group at 3 months (71 ± 7 versus 72 ± 11, mean difference 1 [95% CI -3.7 to 5.7]; p = 0.07) or at 6 months after surgery (76 ± 6 versus 79 ± 11, mean difference 3 [95% CI -3.5 to 7.9]; p = 0.12). There were no differences in surgical duration or radiation doses between the intraoperative referencing and control groups. We found only a small advantage in favor of the intraoperative referencing system in terms of loss of reduction on ulnar variance (3 months after surgery: 0.2 ± 0.4 mm versus 0.6 ± 0.7 mm, mean difference 0.4 mm [95% CI 0.15 to 0.69]; p = 0.003, 6 months after surgery: 0.4 ± 0.6 mm versus 0.8 ± 0.8 mm, mean difference 0.4 mm [95% CI 0.05 to 0.73]; p = 0.02 for the intraoperative referencing system and the control group, respectively). This difference in radial shortening was so small that it was not likely to have been clinically important.

Conclusion We found no clinically important advantages from the use of our novel intraoperative referencing system except a slight improvement in ulnar variance. Therefore, we recommend against its use in everyday practice at this time. However, future improvements may lead to better clinical outcomes, so we plan further investigations.

Level of Evidence Level III, therapeutic study.

Introduction

Distal radius fractures are common, representing 44% of all fractures [7]; they occur most often in elderly patients after low-energy trauma and in young patients after high-energy trauma. Peak incidence is in Caucasian women older than 65 years [4]. Distal radius fractures can be treated either nonsurgically or with reduction and fixation. Although many patients treated nonsurgically report little pain or disability, there is evidence that the risk of redisplacement is up to 64% in those treated conservatively [9]. Generally, those patients with a dorsal angulation greater than 15°, radial shortening larger than 3 mm, or an intra-articular stepoff greater than 2 mm are indicated for surgical treatment to have better results, both in terms of achieving an anatomic reduction and clinical outcomes [11].

Anatomic fracture reduction provides a better chance of full functional restoration, since the risk of developing posttraumatic osteoarthritis is 20-fold higher for intra-articular fractures [1], and a residual articular stepoff of more than 2 mm results in posttraumatic osteoarthritis in 100% of patients [9]. Preoperative planning is performed to simulate the process of reduction as well as the size and placement of implants. This commonly is done using picture archiving and communication systems (PACS) [3]. However, this does not allow for planning in three dimensions (3D). We previously developed and reported a 3D digital preoperative planning system for the osteosynthesis of distal radius fractures [17]. The initial version of this system did not allow direct comparison of preoperative planning and intraoperative fluoroscopic images, so we developed a novel intraoperative referencing system that superimposes preoperative planning onto fluoroscopic images during surgery [19]. However, whether this new system provides benefits that patients can perceive has not been evaluated.

We therefore asked: Does use of our novel intraoperative referencing system result in (1) better Mayo wrist scores at 3 and 6 months after surgery and (2) less loss of reduction in terms of ulnar variance, palmar tilt, and radial inclination on plain radiographs taken 1 week, 3 months, and 6 months after surgery compared with conventional preoperative planning?

Patients and Methods

Study Design and Setting

This was a single-center, retrospective, comparative study that used propensity matching. Our institution is a core hospital in a city with a population of 50,000 that supports a wide variety of both community and referral patients from surrounding rural area.

Patients and Propensity Score Matching

Between April 2014 and October 2021, we treated 294 patients with open reduction and volar plate fixation for distal radius fractures. Of 294 patients, 65% (191) underwent surgery using either conventional preoperative planning or our novel intraoperative referencing system. The remaining patients were excluded because they were younger than 18 years, they had some missing medical records related to clinical outcomes, or they had a previous history of upper extremity injuries. During that time, we generally treated fractures with volar plates when there was more than 2 mm of stepoff/gap in the articular surface, a dorsal tilt more than 15°, radial inclination less than 15°, or radial shortening more than 5 mm. Usually, we used a flexor carpi radialis approach. In some patients with dorsal fragments, we added a dorsal approach.

As we were developing our novel intraoperative referencing system, which at this time is called the image fusion system, we used it inconsistently. We started consistently using the new system in July 2018.

We divided patients into two groups: the intraoperative referencing group and the control group. We used our novel intraoperative referencing system and the 3D digital preoperative planning system for preoperative planning in the intraoperative referencing group. Currently, this program is not commercially available. This program is in development with a software company (LEXI Co Ltd). In this study, we collected the data using the program to obtain a proof of concept. Preoperative planning was performed manually in the conventional manner using tracing paper and implant templates or using a digital template in the control group.

To arrive at a fair assessment, we opted to perform propensity matching based on age, gender, and AO fracture type (assessed on CT scans). During the time period in question, 36% (69 of 191) of patients with distal radius fractures who received a volar plate were treated using our novel intraoperative referencing system and 64% (122 of 191) had surgery using conventional preoperative planning (control group). Of those, 91% (63 of 69) of patients in the intraoperative referencing system group and 89% (108 of 122) of those in the control group were available for follow-up with all imaging and Mayo wrist scores at least 6 months after surgery. We used a nearest neighbor matching model to create a comparable control group. The matching variables of age and fracture type were inserted for a propensity score matching algorithm with one-to-one optimum matching between the two groups. Propensity matching left us with two groups each with 39 patients. We also tried to match patients based on gender, but because there were fewer patients in the intraoperative referencing group, the percentage of women for each group differed: 70% (44 of 63) for the intraoperative referencing group and 76% (82 of 108) for the control group. Also, there were fewer men with C3 fractures in the control group, with 21% (13 of 63) in the intraoperative referencing group and 9% (10 of 108) in the control group (Table 1). After propensity matching, the intraoperative referencing group was comprised of 64% (25 of 39) women and the control group included 77% (30 of 39) women.

Descriptive Data

Our two study groups did not differ in important ways after we applied propensity score matching in terms of age, gender, and fracture type (Table 2). The study population included 25 women and 14 men in the intraoperative referencing group with a mean age of 65 ± 14 years. In the control group, there were 30 women and 9 men with a mean age of 66 ± 12 years.

Preoperative Planning

We planned to use Stellar P/D locking plates (HOYA Technosurgical Inc) for all patients. This plate system is a monoaxial volar locking plate system and has three sizes for width (small, medium, and large) and two sizes for length (short and long). Distal screw lengths varied from 10 to 24 mm with a diameter of 2.4 mm, and proximal screw lengths varied from 10 to 20 mm with a diameter of 2.6 mm.

Details on preoperative planning using our novel intraoperative referencing system were previously reported [19]. Using the system, contours of bones and implants from the preoperative plan were extracted, and they could be superimposed to intraoperative fluoroscopic images. So the system enables the surgeons to refer to the overlapping images to determine implant placement. We performed preoperative planning in the control group by handwriting on tracing paper and adjusting the scale of the AP and lateral views of radiographs on PACS or using a digital template [17]. Radiographs of the contralateral side were used. The size and placement of the locking plate were planned in both groups. The surgical goals were identical in

Table 1. Proportion of patients before propensity matching

Fracture type	Intraoperative referencing group (n = 63)	Control group (n = 108)
A2		
Women	2 (1)	1 (1)
Men	0 (0)	0 (0)
A3		
Women	19 (12)	15 (16)
Men	0 (0)	3 (3)
B3		
Women	2 (1)	3 (3)
Men	2 (1)	1 (1)
C1		
Women	2 (1)	0 (0)
Men	0 (0)	2 (2)
C2		
Women	22 (14)	31 (34)
Men	8 (5)	9 (10)
C3		
Women	24 (15)	26 (28)
Men	21 (13)	9 (10)

Data presented as % (n).

both groups, in terms of anatomical reduction, plate placement, and prevention of screw protrusion either dorsally or intraarticularly.

Surgical Technique and Aftercare

After preoperative planning, we performed osteosynthesis in all patients under general anesthesia. In the intraoperative referencing system group, the outline of the planned image was displayed on a fluoroscopy monitor, and its size was calibrated and overlapped with the fluoroscopic image (Fig. 1). Surgeons made an effort to reproduce the planned reduction and implant position in accordance with the outline of the intraoperative referencing system, and they referred to the handwritten preoperative plan in the control group. Both groups underwent the same postoperative rehabilitation program. We immobilized the wrist with a splint for 1 to 2 weeks, then initiated ROM exercises of the wrist and forearm under the instruction of hand therapists. ROM exercises of fingers were initiated soon after surgery.

Table 2. Characteristics of included patients

	Intraoperative referencing group (n = 39)	Control group (n = 39)	p value
Women	64 (25)	77 (30)	0.21
Age in years	65 ± 14	66 ± 12	0.44
AO classification			0.63
A3	15 (6)	13 (5)	
B3	3 (1)	3 (1)	
C2	49 (19)	56 (22)	
C3	33 (13)	28 (11)	

Data presented as % (n) or mean ± SD.

Data Sources and Measurement

We assessed the surgical duration, radiation dose needed in surgery, and Mayo wrist scores 3 and 6 months after surgery. The presence or absence of complications in each group was recorded at the time of the final hospital visit. All data were abstracted from the medical records by one surgeon who participated in the study (YY); this surgeon was not blinded to the study groups. In addition, the number of distal screws protruding into the joint or dorsal compartment was assessed by radiograph and CT. We took postoperative CTs 1 month after surgery. Bearing in mind the patients' radiation exposure, we took CT scans with patients standing with both hands in front to reduce the absorbed radiation dose. We also used the Advanced intelligent Clear-IQ Engine application (Canon Medical Systems) for low-dose imaging during CT scans, which resulted in a reduction of the CT dose index from the conventional 6.9 mGy to 1.4 mGy. We assessed the loss of reduction on ulnar variance, palmar tilt, and radial inclination on plain radiographs taken 1 week, 3 months, and 6 months after surgery. Two raters (YY and one individual who was not a study author) independently assessed images. The second rater was blinded to the groups. Interrater reliabilities were excellent [2], with intraclass correlation coefficient values of 0.97, 0.88, and 0.91 for ulnar variance, palmar tilt, and radial inclination, respectively. After evaluating the reliability of the two raters' measurements, the mean values for each parameter were used in further analyses.

Primary and Secondary Study Outcomes

Our primary study goal was to evaluate the usefulness of our novel intraoperative referencing system on clinical outcomes. To achieve this, we evaluated Mayo wrist scores 3 and 6 months after surgery and compared them with the results of patients who underwent surgery with conventional preoperative planning.

Our secondary study goal was to clarify the effect of our novel intraoperative referencing system on radiological parameters. To achieve this, we assessed the loss of reduction in terms of ulnar variance, palmar tilt, and radial inclination

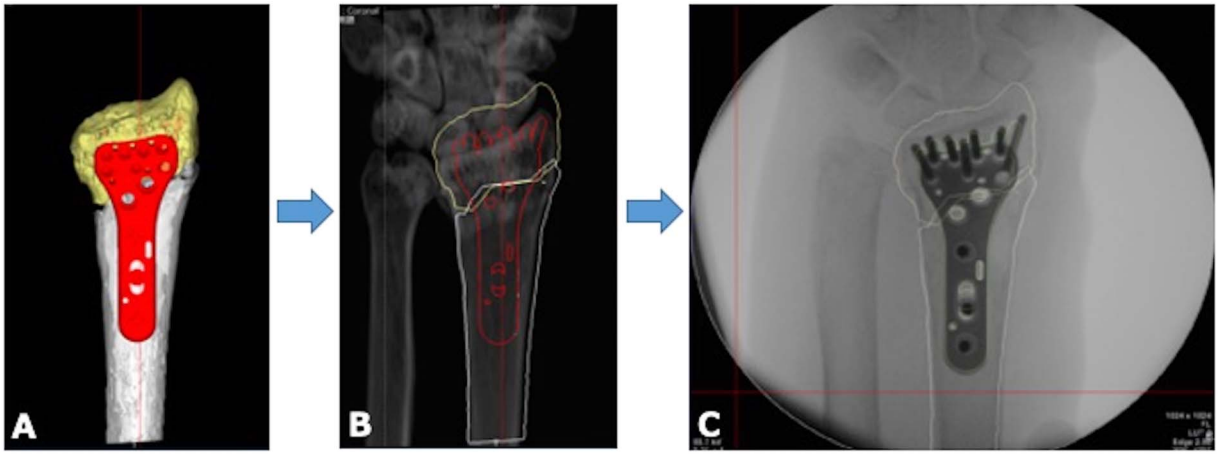

Fig. 1 The image fusion system is shown here. (**A**) Preoperative planning is done using a 3D digital preoperative planning system. (**B**) Contours were extracted from the preoperative 3D planning. (**C**) Extracted contours were superimposed onto intraoperative fluoroscopy images.

with the differences of the measurements between radiographs taken at 3 months and 6 months after surgery and radiographs taken at 1 week after surgery. We compared these findings with the results of patients who underwent surgery with conventional preoperative planning.

Ethical Approval

The study protocol was approved by the institutional review board of Tokyo Medical University (T2019-0178 and T2022-0041) and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. Informed consent for surgery and for using the medical records was obtained from all patients included in the study at the time of admission. For access to the medical record in previous cases, the outline of research was published on the hospital's website to ensure that patients had the opportunity to decline the use of their data for the study.

Statistical Analysis

Results are expressed as the mean ± SD. A loss of reduction was defined as the difference between the values measured 1 week after surgery and those measured 3 and 6 months after surgery. Each item was compared between the intraoperative referencing and control groups using the Welch t-test. Screw protrusions were also compared between groups with the chi-square test. Differences were considered significant when p values were less than 0.05. All statistical analyses were performed using BellCurve for Excel version 2.12 (SSRI Co.) and SPSS 28 statistics (IBM Co.).

Results

Mayo Wrist Scores and Other Clinical Outcomes

Mayo wrist scores were no different between the intraoperative referencing system and the control group at 3 months (71 ± 7 versus 72 ± 11, mean difference 1 [95% CI -3.7 to 5.7]; p = 0.07) or at 6 months after surgery (76 ± 6 versus 79 ± 11, mean difference 3 [95% CI -3.5 to 7.9]; p = 0.12) (Fig. 2).

There were no differences in surgical duration or radiation dose. Surgical duration was 105 ± 35 and 94 ± 25 minutes in the intraoperative referencing system and control groups, respectively (p = 0.10). Radiation doses were 4.8 ± 2.3 mGy and 5.5 ± 3.1 mGy in the intraoperative referencing system and control groups, respectively (p = 0.33).

Three patients experienced nerve-related complications (one patient developed carpal tunnel syndrome and two patients had symptoms of median nerve palmar branch injury) in each group. Two patients in the intraoperative referencing system and three patients in the control group had wrist pain, and two patients in the intraoperative referencing system and one patient in the control group had symptoms related to wound scars. There were no between-group differences in terms of the number of distal screws protruding into the joint; there was one in the intraoperative referencing system group (total number of distal screws: 276) and five in the control group (total number of distal screws: 278; p = 0.10). Likewise, there were no between-group differences in the number of distal screws protruding into the dorsal extensor tendon compartment; there were 14 in the intraoperative referencing system group and 11 in the control group (p = 0.52).

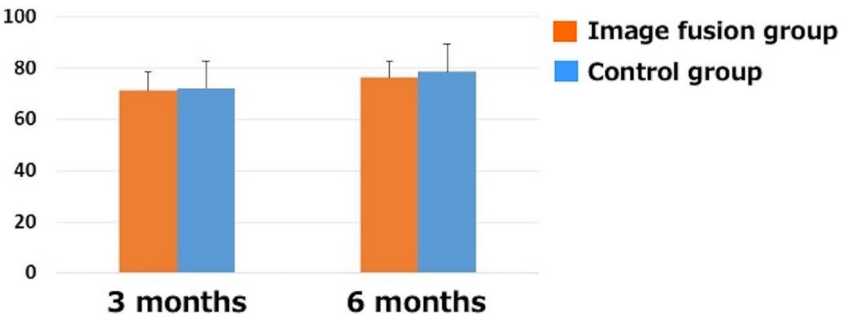

Fig. 2 Mayo wrist scores recorded at 3 and 6 months after surgery show no differences between the image fusion and control groups.

Loss of Reduction

We found no advantage to using the intraoperative referencing system in terms of loss of reduction in palmar tilt (3 months after surgery: 1.5° ± 1.5° versus 1.5° ± 1.3°, mean difference 0.0° [95% CI -0.6° to 0.6°]; p = 0.73, 6 months after surgery: 1.3° ± 1.0° versus 1.4° ± 1.4°, mean difference 0.1° [95% CI -0.4° to 0.6°]; p = 0.71 for the intraoperative referencing system and the control group, respectively) or radial inclination (3 months after surgery: 1.2° ± 0.8° versus 1.0° ± 0.8°, mean difference 0.2° [95% CI -0.2° to 0.5°]; p = 0.38, 6 months after surgery: 1.2° ± 1.2° versus 1.3° ± 1.0°, mean difference 0.1° [95% CI -0.4° to 0.6°]; p = 0.69 for the intraoperative referencing system and the control group, respectively). We found only a small advantage to the intraoperative referencing system in terms of loss of reduction on ulnar variance (3 months after surgery: 0.2 ± 0.4 mm versus 0.6 ± 0.7 mm, mean difference 0.4 mm [95% CI 0.15 to 0.69]; p = 0.003, 6 months after surgery: 0.4 ± 0.6 mm versus 0.8 ± 0.8 mm, mean difference 0.4 mm [95% CI 0.05 to 0.73]; p = 0.02 for the intraoperative referencing system and the control group, respectively) (Fig. 3). This difference in radial shortening was so small that it was not likely to have been clinically important.

Discussion

Volar locking plate fixation has been widely used for distal radius fractures since it was introduced in 2000 [12]. A plate must be placed properly to provide sufficient subchondral support [6, 8, 10]. Fragment-specific fixation is considered important when a fracture is comminuted [7]. We previously demonstrated that the reproducibility of the distance between the distal end of the volar locking plate

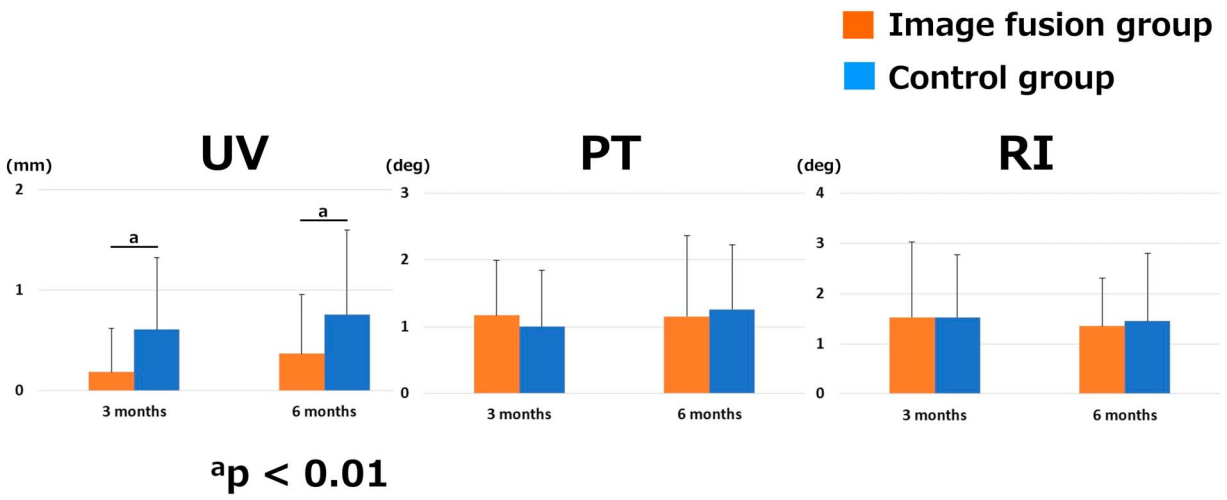

Fig. 3 In this graph, which shows the loss of reduction 3 and 6 months after surgery, the loss of ulnar variance was greater in the control group. However, no differences were observed in radial inclination or palmar tilt between the groups; UV = ulnar variance; RI = radial inclination; PT = palmar tilt.

and joint surface by our intraoperative referencing system was high [19]. We believe that precise 3D preoperative planning and intraoperative reference to the planning may enable surgeons to achieve better anatomic fracture reduction, leading to a better chance of full functional restoration. We aimed to assess whether our novel intraoperative referencing system provides patient-perceived benefits. Our results suggest that the system prevented postoperative radial shortening; however, we observed no differences in clinical outcomes between the intraoperative referencing and control groups.

Limitations

There are several study limitations that must be addressed. Even though our novel intraoperative referencing system is easy to use, a specific application needs to be installed on the computer, which is an additional cost. Second, we did not subanalyze the patients by gender. The results drawn from the study may not be applied separately to men and women. In addition, we included patients from a wide range of ages, and the clinical results among these varying age groups may differ. We did not have enough patients to evaluate this, so we will work on it in the future. Third, since this is a retrospective study, we cannot completely exclude the possibility of selection bias. For example, the patients in the control group were enrolled earlier in the study period, whereas the patients in the intraoperative referencing group were recently treated cases. We could not avoid this selection bias because our intraoperative referencing system had not launched when we started collecting patients. In addition, we used the AO classification for the propensity matching. However, there can be a wide range of displacement and damage among the same AO fracture types. In the future, we need to take these into consideration. Fourth, we have used only a single type of volar locking plate system with the flexor carpi radialis approach. Our results may vary with different locking plate systems or surgical approaches. Fifth, our novel intraoperative referencing system is not yet commercially available. We are developing this program with a software company (LEXI Co Ltd). Some modifications may be necessary based on the results of this study. Finally, we believe that a follow-up period of 6 months would be sufficient to demonstrate a difference in treatment of distal radius fractures, but a longer follow-up period may affect clinical outcomes. We will continue to accumulate data for future investigations.

Mayo Wrist Scores and Other Clinical Outcomes

There was no clinical benefit to using the intraoperative referencing system as measured by the Mayo wrist score at either 3 or 6 months after surgery. There were no differences in operative duration, radiation dose, and the complication rate. Therefore, this system currently is unlikely to offer value to patients in terms of any endpoints they are likely to perceive.

Loss of Reduction

We found no difference in loss of reduction in terms of radial inclination or palmar tilt at 3 or 6 months, although there was slightly less loss of reduction in ulnar variance for the intraoperative referencing system group at both 3 and 6 months. This difference in ulnar variance was so small that it did not result in any differences in clinical outcomes.

Other Relevant Findings

Appropriate subchondral support is important not only for radial shortening but also for angular stability [6, 8, 10]. The results we obtained in this study were only a matter of several millimeters; therefore, we do not know whether overall stability was higher in the intraoperative referencing group. The present study included a wide variety of fractures. The results may have differed if we had evaluated only comminuted fractures, but this is speculative. Future studies might evaluate systems like ours in a study limited to comminuted fractures. Greater stability, if it can be achieved, might allow more aggressive postoperative rehabilitation.

Nerve-related complications, such as carpal tunnel syndrome after the osteosynthesis of distal radius fractures using volar locking plates, may have been associated with improper plate positioning [5, 15]. Carpal tunnel syndrome occurs in between 2% and 9% of patients in this setting [5, 16], and in this study, it occurred in 3% of both groups. Inappropriate plate positioning has also been reported to cause intra-articular screw protrusion, especially with monoaxial volar locking plate systems [13]. In the present study, there was no between-group difference in terms of the number of screws protruding into the joint, but we were underpowered on that endpoint. Future studies, perhaps multicenter collaborations, would be needed to determine whether there is any advantage to this system in terms of screw protrusion, and if there is, whether it is large enough to justify the costs of the system.

Our intraoperative referencing system can be used as an educational tool for young surgeons. It may help surgeons predict how each fragment should be reduced based on preoperative planning and perform fragment-specific fixation. For less-experienced surgeons, intraoperative referencing systems like this one may facilitate teaching and learning about fracture reduction and plate position. However, before it can be widely adopted for this purpose, its benefits would need to be validated in studies about surgical learning curves and accuracy of plate and screw position.

Conclusion

We found no clinically important advantages from the use of our novel intraoperative referencing system except a slight improvement in ulnar variance. No differences were observed in clinical outcomes, operative duration, or radiation doses between the intraoperative referencing system and control groups. We recommend against the use of this intraoperative referencing system in everyday practice in its current form. We now are modifying this system with 3D tracking and 3D reconstructions of the fluoroscopic images, and we plan to re-evaluate it after we have done so [14, 18].

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ACUTE MEDICINE & SURGERY WILEY

CASE REPORT

Intoxication with massive doses of amlodipine and candesartan requiring venoarterial extracorporeal membrane oxygenation

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Abstract

Background: Calcium channel blockers and angiotensin II receptor blockers are commonly prescribed to treat hypertension. Massive overdoses can cause both distributive and cardiogenic shock because of their effects on vascular smooth muscles and severe myocardial depression.

Case Presentation: We present the case of a 46-year-old man who was brought to our emergency department after ingesting 1210 mg amlodipine and 936 mg candesartan. The patient's hemodynamic status deteriorated despite treatment with vasopressors, calcium gluconate, and hyperinsulinemia-euglycemia therapy with mechanical ventilation. Venoarterial extracorporeal membrane oxygenation was initiated for refractory shock. The patient was weaned off extracorporeal membrane oxygenation on day 5 and discharged on day 18 of hospitalization.

Conclusion: When medical therapies are ineffective, aggressive venoarterial extracorporeal membrane oxygenation should be considered for the management of refractory shock in the setting of calcium channel blocker with angiotensin II receptor blocker overdose.

KEYWORDS
amlodipine, candesartan, drug overdose, ECMO, toxicity

INTRODUCTION

An overdose of calcium channel blockers (CCBs) can cause life-threatening hypotension, for which vasopressors might not be effective. Here, we present a case of drug-refractory hypotension caused by a massive overdose of CCBs and angiotensin II receptor blockers (ARBs). The patient was successfully managed with venoarterial extracorporeal membrane oxygenation (VA-ECMO).

CASE PRESENTATION

A 46-year-old man was brought to our emergency department with general malaise 14 h after ingesting 1210 mg amlodipine besylate (amlodipine) and 936 mg candesartan cilexetil (candesartan) in a suicide attempt. He had a history of hypertension, but no known history of mental illness. Upon arrival at the emergency department, his vital signs were as follows: Glasgow Coma Scale score, 13 (E3V4M6); blood pressure, 60/39 mmHg; heart rate, 95 b.p.m. (sinus rhythm); respiratory rate, 30 breaths/min; and blood oxygen saturation, 93% on a reservoir oxygen mask at 10 L/min. Blood tests revealed elevated lactate concentration and metabolic acidosis (Table 1). The 12-lead electrocardiogram findings were as follows: heart rate, 91 b.p.m.; normal sinus rhythm; right bundle branch block; and no QTc prolongation. The transthoracic echocardiogram findings were as follows: visually estimated ejection fraction, 20%; no asynergy; and no valvular disease.

TABLE 1 Laboratory findings on day 1 of hospitalization of a 46-year-old man with intoxication with massive doses of amlodipine and candesartan

Hematology			**Coagulation**		
WBC	18,100/μL	(3,500–8,500)	PT-INR	0.98	(0.9–1.1)
RBC	490 × 10/μL	(430–570)	APTT	25.9 s	(28.0–42.0)
Hb	14.7 g/dL	(11.5–15.0)	Fbg	575 mg/dL	(150–400)
Plt	27.0×10^4/μL	(15.0–35.0)	D-dimer	0.8 μg/mL	(<1.0)
Biochemistry			**Arterial blood gas (Oxygen 10 L/min)**		
T-Bil	0.7 mg/dL	(0.3–1.2)	pH	7.299	(7.35–7.45)
AST	32 U/L	(10–40)	pCO_2	31.6 mmHg	(35–45)
ALT	48 U/L	(5–40)	pO_2	98.6 mmHg	(80–100)
γ-GTP	55 U/L	(15.0–35.0)	HCO_3^-	15.2 mmol/L	(20–26)
BUN	92.6 mg/dL	(8–22)	BE	−9.9 mmol/L	(−3 to 3)
Cre	2.60 mg/dL	(0.47–0.79)	Na	139 mEq/L	(135–148)
CK	80 U/L	(62–287)	K	4.0 mEq/L	(3.5–5.3)
CRP	0.05 mg/dL	(<0.3)	Cl	103 mEq/L	(98–106)
Na	138 mmol/L	(138–145)	Ca	1.24 mmol/L	(1.13–1.32)
K	4.1 mmol/L	(3.6–4.8)	AnGap	25 mmol/L	(10–18)
Cl	106 mmol/L	(101–108)	Glucose	238 mg/dL	(70–110)
Ca	9.9 mg/dL	(8.8–10.1)	Lactate	7.8 mmol/L	(0.5–2.0)

Note: Normal range of values shown in parentheses.

Abbreviations: ALT, alanine transaminase; AnGap, anion gap; APTT, activated partial thromboplastin clotting time; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; Ca, calcium; CK, creatine kinase; Cl, chloride; Cre, creatinine; CRP, C-reactive protein; Fbg, fibrinogen; Hb, hemoglobin; HCO_3^-, bicarbonate; K, potassium; Na, sodium; pCO_2, partial pressure of carbon dioxide; Plt, platelet; pO_2, partial pressure of oxygen; PT-INR, prothrombin time international normalized ratio; RBC, red blood cell; T-Bil, total bilirubin; WBC, white blood cell; γ-GTP, gamma-glutamyl transferase.

Based on the patient's medical history, we suspected acute amlodipine and candesartan intoxication that led to shock. However, despite our attempts to improve his condition with fluid resuscitation and the administration of high-dose noradrenaline and vasopressin, there was no improvement in the patient's blood pressure or lactic acidosis. To maintain the patient's blood calcium levels, we administered calcium gluconate and regularly monitored the levels using arterial blood gas tests. Hyperinsulinemia-euglycemia therapy was initiated at a rate of 0.5 U/kg/h, without a bolus to avoid hypoglycemia and hypokalemia. Additionally, we administered lipid emulsion and glucagon. Unfortunately, the patient's vital signs, ejection fraction, and left ventricular outflow tract velocity time integral showed no improvement. We considered using methylene blue, but it was unavailable at our hospital.

In addition to distributive shock, we suspected impaired cardiac function contributing to the catecholamine-refractory hypotension, suggesting cardiogenic shock. Consequently, we decided to intubate the patient and initiate VA-ECMO approximately 4 h after arrival. Following the initiation of VA-ECMO, we observed a gradual improvement in blood lactate concentration and metabolic acidosis, and we simplified our management approach by discontinuing hyperinsulinemia-euglycemia therapy, lipid emulsion, and glucagon.

Despite the improvement observed with VA-ECMO, the patient still required catecholamines for several days to maintain mean arterial pressure, indicating persisting refractory distributive shock. Over time, the patient's requirement for catecholamines decreased, and cardiac function gradually improved, ultimately leading to successful weaning from VA-ECMO on day 5 of hospitalization. Although the patient experienced renal failure due to the intoxication, renal replacement therapy was not deemed necessary. Finally, the patient was extubated on day 9 and discharged on day 18 without experiencing any complications related to VA-ECMO. Blood levels of amlodipine and candesartan were determined. The maximum blood concentrations of amlodipine and candesartan were 536.9 and 8.1 mg/mL, respectively, on day 1 (Figure 1).

DISCUSSION

We encountered a patient with hypotension refractory to drug therapy, due to the co-ingestion of massive doses of amlodipine and candesartan, in whom VA-ECMO played a life-saving role.

Amlodipine is a CCB belonging to the class of dihydropyridines that exerts antihypertensive effects by acting on vascular smooth muscles. It is characterized by a long duration of action, taking 7.6 ± 1.8 h to reach maximum blood concentration, and has an elimination half-life of 34 ± 5 h.[1] Dihydropyridines are highly selective for vascular smooth muscles; however, when administered excessively, they may lose their selectivity and act on the myocardium, resulting in a negative inotropic effect.[2] In addition, the extent of amlodipine's antihypertensive effects is based on its serum concentrations.[3] Fatal cases have been reported at doses of 70 mg

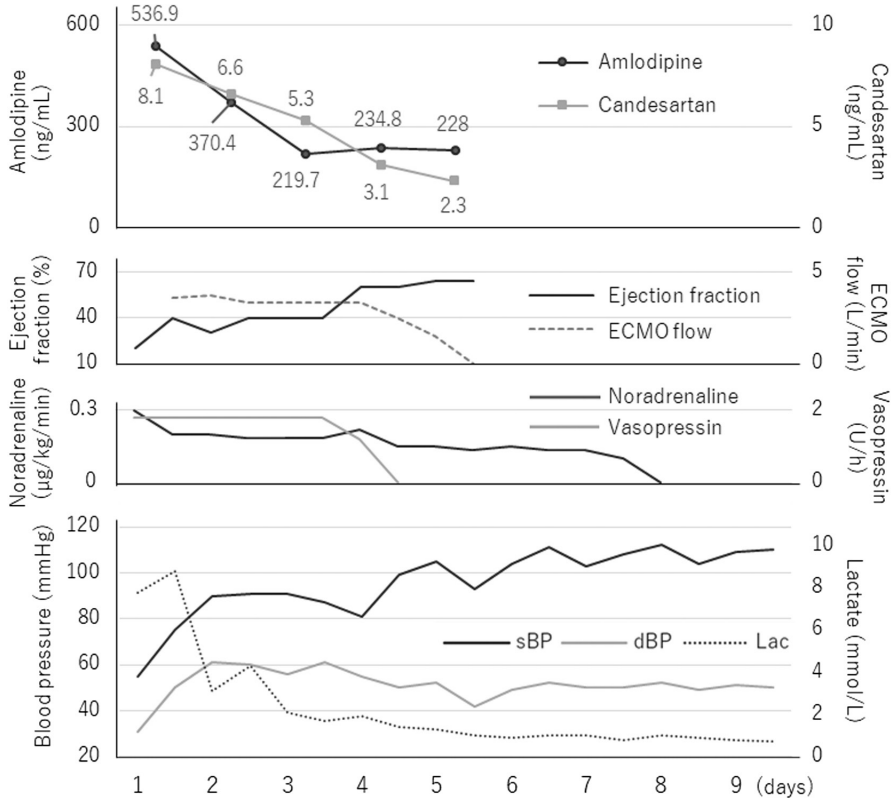

FIGURE 1 Blood concentrations of amlodipine and candesartan during the clinical course of a 46-year-old man with intoxication with massive doses of amlodipine and candesartan. dBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; Lac, lactate; sBP, systolic blood pressure.

and serum drug concentrations of 185 μg/L.[4] In this case, the serum drug concentration (536.9 μg/L) was extremely high compared to that in previous reports. Therefore, the patient may have experienced both cardiogenic and distributive shock. Worldwide, cases of survival and discharge after oral ingestion of doses exceeding 1000 mg are extremely rare,[5] and a PubMed search found no case report in the past 30 years of a patient discharged alive after taking more than 1200 mg amlodipine. Therefore, to the best of our knowledge, the oral dose of amlodipine (1250 mg) ingested by our patient is the highest among all reported survival cases.

Angiotensin II receptor blockers inhibit vasoconstriction and reduce peripheral vascular resistance and blood pressure by directly blocking the angiotensin II type 1 receptor, the primary target of angiotensin II. Symptoms of ARB intoxication include hypotension, nausea/vomiting, dizziness, fatigue, and somnolence. Severe symptoms are uncommon, and according to a case series of 206 ARB overdoses, only one pediatric patient required intravenous fluids for treatment.[6] Moreover, long-term use of ARBs can lead to decreased sensitivity to hormones that regulate blood pressure, resulting in catecholamine-refractory hypotension.[7]

In addition, regarding the interaction between CCBs and ARBs, the vasodilating effect of CCBs is compensated for by the activity of the renin-angiotensin system, but suppression of this compensatory effect by ARBs contributes to severe hypotension.[8] Indeed, as previously reported by Huang et al.[8] the combined overdose of dihydropyridines and ARBs resulted in more severe hypotension and required greater hemodynamic support compared with overdosing on dihydropyridines alone.

The treatment of acute poisoning with amlodipine is based on systemic management, including airway, respiratory, and circulatory control. There are several specific treatment methods to cope with distributive shock due to vasodilation, such as calcium and glucagon administration, high-dose insulin therapy, and lipid emulsion therapy. However, as in this case, if the patient develops refractory shock, VA-ECMO has the potential to improve the patient's hemodynamic and metabolic status. In 2021, Upchurch et al.[9] recommended the consideration of VA-ECMO in the absence of contraindications for all patients with acute poisoning and refractory cardiogenic shock. In fact, the use of VA-ECMO for treating drug intoxication, including several cases of amlodipine intoxication, has increased in recent years.[9]

Similar to drug-induced refractory shock, septic shock causes a condition that can result in simultaneous cardiogenic and distributive shock. In recent years, VA-ECMO has been found to be effective for distributive shock. Falk et al.[10] reported that VA-ECMO may be beneficial for both the hospital and long-term survival of patients with distributive septic shock. They argued that VA-ECMO supports the failing heart but does not directly impact other parts causing hypotension; however, improving tissue oxygenation may

play a role in stabilizing circulation and limiting the negative impact of generalized poor oxygenation.

Consequently, the active management of patients with drug-refractory hypotension using VA-ECMO appears to be a reasonable strategy.

CONCLUSION

Venoarterial extracorporeal membrane oxygenation can be used in patients with severe cardiogenic and distributive shock caused by massive overdoses of CCBs and ARBs.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of Interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: N/A.
Informed consent: Informed consent for the publication of this case report was obtained from the patient.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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Original Article

Excess mortality in COVID-19-affected solid organ transplant recipients across the pandemic

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ABSTRACT

The excess mortality of coronavirus disease 2019 (COVID-19) solid organ transplant recipients (SOTRs) throughout the pandemic remains unclear. This prospective cohort study based on the Japanese nationwide registry included 1632 SOTRs diagnosed with COVID-19 between February 1, 2020, and July 31, 2022, categorized based on dominant phases of variants of concern (VOCs): Waves 1 to 3 (Beta), 4 (Alpha), 5 (Delta), 6 (Omicron BA.1/BA.2), and 7 (Omicron BA.5). Excess mortality of COVID-19-affected SOTRs was analyzed by calculating standardized mortality ratios (SMRs). Overall, 1632 COVID-19-confirmed SOTRs included 1170 kidney, 408 liver, 25 lung, 20 heart, 1 small intestine, and 8 multi-organ recipients. Although disease severity and all-cause mortality decreased as VOCs transitioned, SMRs of SOTRs were consistently higher than those of the general population throughout the pandemic, showing a U-shaped gap that peaked toward the Omicron BA.5 phase; SMR (95% CI): 6.2 (3.1-12.5), 4.0 (1.5-10.6), 3.0 (1.3-6.7), 8.8 (5.3-14.5), and 21.9 (5.5-87.6) for Waves 1 to 3 (Beta), Wave 4 (Alpha), Wave 5 (Delta), Wave 6 (Omicron BA.1/

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HER-SYS, Health Center Real-Time Information-sharing System; HLA, human leukocyte antigen; ICU, intensive care unit; JST, Japan Society for Transplantation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMRs, standardized mortality ratios; SOTRs, solid organ transplant recipients; VOC, variants of concern.

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2), and Wave 7 (Omicron BA.5), respectively. In conclusion, COVID-19 SOTRs had greater SMRs than the general population across the pandemic. Vaccine boosters, immunosuppression optimization, and other protective measures, particularly for older SOTRs, are paramount.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has severely affected organ transplantation worldwide, considerably reducing patient life-years in solid organ transplant recipients (SOTRs) due to the increased risks of severe disease and mortality.[1-3] The in-hospital mortality rate of COVID-19–related pneumonia was 2.5-fold higher than that of non-COVID-19–related pneumonia among SOTRs.[4] In Japan, in the early period of the COVID-19 pandemic, the number of deceased donor organ donations and transplantations dropped to 61% and 69%, respectively, of the year-on-year average (2019 vs 2020),[5] and living donor kidney transplantation was particularly affected due to its nonurgent nature and lack of deceased donors.[6] Despite measures and therapeutics being implemented to restore transplant activities, cautionary measures are still required due to the suboptimal immunogenicity of SARS-CoV-2 vaccines in SOTRs[7,8] and the high infectivity of the Omicron variant of concern (VOC).[9]

Previous studies have delineated the short-term outcomes of COVID-19-affected SOTRs, but mostly in the early phase and with a limited follow-up period.[2,10] Furthermore, although guidelines published by transplant societies, including the Japan Society for Transplantation (JST), have recommended treatment options, most pivotal trials for therapeutics have excluded SOTRs.[3] Accordingly, the excess mortality due to COVID-19 among SOTRs compared to the general populations across the pandemic has yet to be elucidated. In the present study, we investigated the detailed epidemiology, interventions, and prognoses over a year-long follow-up period to reveal the excess mortality due to COVID-19 among SOTRs throughout the pandemic period.

2. Methods

This study was conducted by the JST COVID-19 Registry Study Group (The author list of the JST COVID-19 Registry Study Group is available in the Supplementary material) involving multiple centers nationwide. The study participants were SOTRs diagnosed with COVID-19 between February 1, 2020, and July 31, 2022. In Japan, SOTRs are actively monitored by the transplant centers and encouraged to contact the centers when they are diagnosed with COVID-19. The inclusion criteria for the participants are shown in Figure 1. The primary survey was sent to 122 programs, including 11, 10, and 33 programs for the heart, lung, and liver, respectively. For the kidney, the primary survey was sent to the programs performing >10 cases/year. Of these,

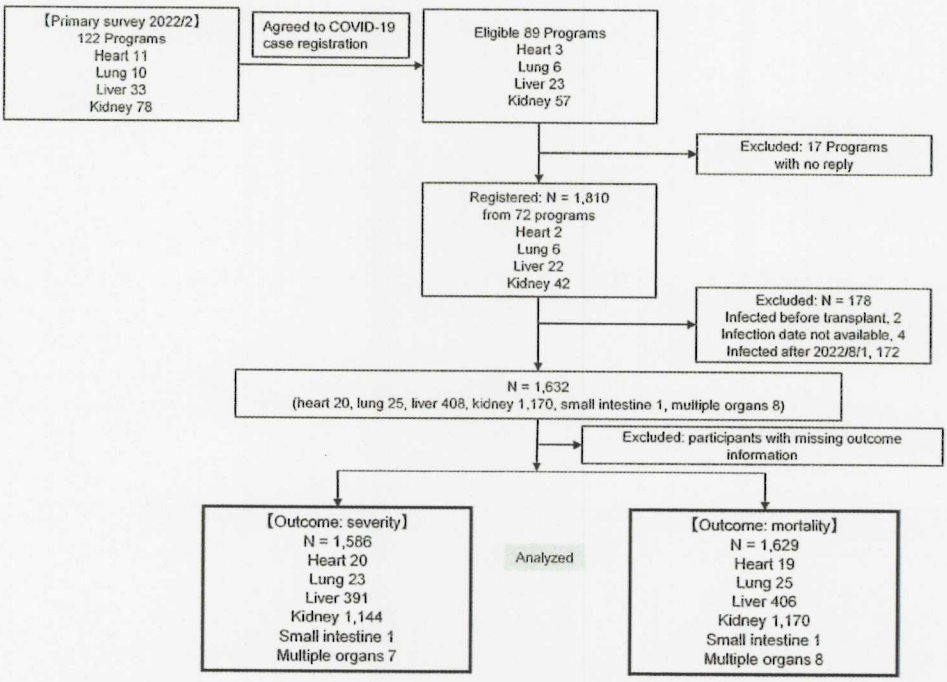


Figure 1. Outline of the study enrolment process. COVID-19, coronavirus disease 2019.

72 programs (2 heart, 6 lung, 22 liver, and 42 kidney programs) were enrolled, with 1632 cases in total. These 72 programs are geographically dispersed high-volume centers responsible for >50% of all de novo organ transplant cases in the country. For example, in 2019, the attending kidney transplant programs performed 56.5% of de novo kidney transplantations in Japan.[11] The questionnaire of this study is available in Supplementary Table S1. The prospectively collected clinical data were analyzed to comprehensively investigate the outcomes of COVID-19 during the pandemic.

2.1. Ethical approval

Ethical approval was obtained from the Institutional Review Board of Kumamoto University, Kumamoto, Japan (approval No. 2504). The requirement for informed consent was waived owing to the noninvasive nature of the study.

2.2. Outcomes

The primary outcome was death up to 1 year after the COVID-19 diagnosis. To capture COVID-19–associated death, deaths within 30, 60, 180, and 365 days after diagnosis with COVID-19 were also considered. Secondary outcomes included hospital admission, intensive care unit (ICU) admission, oxygen demand, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), graft loss within 1 year, and the severity. Other outcomes included acute kidney injury, need for hemodialysis, pneumonia (diagnosed by chest imaging), secondary infection (bacterial, viral, and fungal), high-flow cannula, noninvasive positive pressure ventilation, cardiovascular events, cerebrovascular events, deep vein thrombosis/pulmonary embolism, acute rejection, development of de novo antihuman leukocyte antigen (HLA) antibody, and long COVID. The severity of COVID-19 was defined as follows: asymptomatic, mild (no oxygen demand and signs of pneumonia on chest imaging), moderate (O_2 demand with a nasal cannula or mask and/or positive for pneumonia on chest imaging), and severe (severe hypoxia requiring a high-flow cannula, noninvasive positive pressure ventilation, mechanical ventilation, ECMO, and/or ICU admission).[12] We defined acute kidney injury according to the Kidney Disease Improving Global Outcomes criteria.[13] Long COVID was defined as symptoms persisting for over 2 months that could not be explained by an alternative diagnosis according to the World Health Organization criteria.[14]

2.3. Statistical analysis

The background characteristics of the study participants were compared according to the VOC-dominant phases. The definitions of the VOC-dominant phases and corresponding waves in Japan were as follows: Wave 1: original strain and Beta VOC (B.1.1) January 29, 2020, to June 9, 2020, Wave 2: Beta VOC (B.1.1.284) June 10, 2020, to October 5, 2020, Wave 3: Beta VOC (B.1.1.214) October 6, 2020, to March 2, 2021, Wave 4: Alpha VOC March 3, 2021 to June 22, 2021, Wave 5: Delta VOC June 23, 2021 to December 14, 2021, Wave 6: Omicron-1 VOC (BA.1/BA.2) December 15, 2021 to June 21, 2022, and Wave 7: Omicron-2 VOC (BA.5) June 22, 2022 to July 31, 2022 (Supplementary Fig. S1). The distribution of variables was compared between groups using the chi-square or Fisher exact tests for categorical data and the Mann–Whitney U and Kruskal–Wallis tests for continuous data. Unless otherwise specified, all continuous data are expressed as medians (interquartile range).

The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated using an indirect method with the age-sex structure of the COVID-19 general population to analyze the excess mortality of COVID-19-affected SOTRs. In Japan, all patients diagnosed with COVID-19 were registered into the Health Center Real-Time Information-sharing System (HER-SYS) on COVID-19, and the weekly number of newly diagnosed patients with COVID-19 and deaths by 10-year age categories and sex were available as Japanese open data.[15] The case-fatality rates of the general population during each VOC-dominant phase, classified according to 10-year age categories and sex, were calculated by using the information from HER-SYS and were defined as the reference for SMR regarding COVID-19–affected SOTRs. The Japanese government tracked all COVID-19 cases until September 2022, which falls within the observation period of the present study. We chose to incorporate 60-day mortality into SMR analysis, aligning with the previous studies investigating short-term outcomes related to acute infectious disease including COVID-19, wherein 60-day mortality is often designated as a primary outcome.[16-18] We conducted sensitivity analyses for validating SMRs using 1-year mortality data after COVID-19 diagnosis or COVID-19–related deaths. Because Japanese open data included reinfected patients among the general population, we included the reinfected SOTR patients in SMR analyses.

Survival of the study participants according to the VOC-dominant phases, transplanted organs, or age categories was estimated using the Kaplan–Meier method, and statistical differences between the curves were assessed using the log-rank test. The follow-up period was calculated from the date of the COVID-19 diagnosis to the date of the last visit to the study hospital or death. If the dates of diagnosis and the last visit to the study hospital were unavailable, the date of admission and the discharge date were used, respectively.

Univariate and multivariate proportional hazard models were employed to calculate crude and adjusted hazard ratios and 95% CIs to investigate the risk factors for death within 60 days after COVID-19 diagnosis. Risk factors for composite outcomes, including moderate or severe COVID-19 or death, were examined by odds ratios and 95% CIs in univariate and multivariate logistic regression models because the date of disease progression to moderate or severe condition was not fully collected. Multivariate models included variables statistically correlating with the outcome in univariate analyses ($P < .05$).

Statistical significance was set at $P < .05$. IBM SPSS Statistics for Windows version 28 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses.

All results were reanalyzed, excluding SOTRs with recurrent infections, for validation.

3. Results

3.1. Baseline characteristics

A total of 21 923 outpatient SOTRs were identified, of which 7.3% (n = 1600) were confirmed cases of COVID-19. Recurrent infections (≥2) were observed in 2.0% (n = 32) of the patients. The baseline characteristics of the patients are summarized in Table 1. The median follow-up period was 125 (33–233) days. The median age of the participants was 48 (35–59) years, and most participants were male (61%). The most common comorbidities included hypertension (56%) and diabetes mellitus (22%). tacrolimus and mycophenolate mofetil were commonly used, and everolimus was used in 19% of the patients. Steroids were used in 76%. Notably, some kidney transplant recipients were maintained using the 4 immunosuppressive drugs. Less than 1% of patients had a history of acute rejection (within 3 months) or administration of either rituximab (within 6 months) or antithymoglobulin (within 3 months) before COVID-19 diagnosis. Approximately >50% received at least 1 vaccine during Wave 5 (Delta), which increased to 84% during Wave 7 (Omicron BA.5).

3.2. Disease severity, mortality, and other outcomes

The major outcomes are summarized in Table 2. The all-cause case-fatality rates at 30 days, 60 days, 6 months, 1 year, and overall were 1.4% (n = 22), 2.1% (n = 35), 2.4% (n = 39), 2.6% (n = 43), and 2.7% (n = 44), respectively. The number of COVID-19–related mortalities was 31 (76%), and fatal events occurred in 61% of patients within 30 days and 97% of cases within 60 days. The rates of hospital admission, ICU admission, pneumonia, oxygen demand, mechanical ventilation, and ECMO decreased over time. Disease severity decreased from 19% in Waves 1 to 3 (Beta) to 2% in Wave 7 (Omicron BA.5).

The 1-year all-cause mortality corresponding to different VOC-dominant phases gradually declined over time, with Kaplan-Meier mortality estimates of 11.2%, 10.6%, 7.4%, 2.7%, and 0.6% for Waves 1 to 3 (Beta), Wave 4 (Alpha), Wave 5 (Delta), Wave 6 (Omicron BA.1/2), and Wave 7 (Omicron BA.5), respectively (Fig. 2A for patient survival by waves, and Fig. 2B for patient survival by age categories). Despite this decline, the SMR remained persistently high in the population of SOTRs who expired within 60 days following COVID-19 diagnosis (Fig. 3), widening the U-shaped gap after the Delta VOC phase that peaked toward the Omicron BA.5 VOC phase. Specifically, SMR (95% CI) values of 6.2 (3.1-12.5), 4.0 (1.5-10.6), 3.0 (1.3-6.7), 8.8 (5.3-14.5), and 21.9 (5.5-87.6) were obtained for Waves 1 to 3 (Beta), Wave 4 (Alpha), Wave 5 (Delta), Wave 6 (Omicron BA.1/2), and Wave 7 (Omicron BA.5), respectively (Supplementary Table S2). The same SMR trends were obtained for the sensitivity analysis limited to the 1-year overall or COVID-19–related mortality. Although the COVID-19–related case-fatality rates for severe cases declined over time, they remained consistently high (>25%) during each phase of COVID-19 infection dominated by a VOC, with rates of 38.9%, 38.5%, 46.2%, 29.7%, and 25.0% during Waves 1 to 3 (Beta), Wave 4 (Alpha), Wave 5 (Delta), Wave 6 (Omicron BA.1/2), and Wave 7 (Omicron BA.5), respectively.

Details of the short- and long-term outcomes of the pandemic are available in Supplementary Table S3. Both short- and long-term outcomes exhibited similar gradual declining trends across all phases of COVID-19. Specifically, long-term outcomes included acute rejection (1%), de novo anti-HLA antibodies (6%), and long COVID (3%). Among the 64 recipients positive for de novo anti-HLA antibodies, 32.8% (n = 21) were confirmed to have donor-specific antibodies.

3.3. Treatment and clinical courses

Changes in therapeutic approaches during the pandemic are shown in Supplementary Figure S2. Remdesivir and molnupiravir were the gold-standard antiviral drugs. Anti-SARS-CoV-2 monoclonal antibodies, tocilizumab, and antithrombotic therapy were used in 27%, 2%, and 13% of patients, respectively.

The evolving patterns of immunosuppression adjustments throughout the pandemic are presented in Supplementary Figure S3. Notably, a considerable decrease in the frequency of calcineurin inhibitors and antimetabolites adjustments was observed over time. Conversely, there was an increase in steroid dosage (including escalated-pulse and dexamethasone-switch regimens) in 15% of cases, but this decreased in the Omicron era.

3.4. Risk factors for moderate/severe disease and mortality

The results of the independent risk factors for moderate or severe COVID-19 or deaths are summarized in Table 3 (details are available in Supplementary Table S4). The multivariate analysis revealed that harmful factors, including age ≥ 60 years or having underlying illnesses, mTORi use, steroid use, or antithymoglobulin use within 3 months before COVID-19 diagnosis, were independent risk factors for moderate/severe COVID-19 or deaths; protective factors included vaccination, Waves 6 (Omicron BA.1/2) and 7 (Omicron BA.5) infection, and age <20 years old. The independent risk factors for mortality within 60 days of COVID-19 diagnosis are summarized in Table 4 (details are available in Supplementary Table S5). In the multivariate analysis, independent risk factors impacting mortality were diagnosis during Wave 7 (Omicron BA.5, protective) and age ≥ 60 years (harmful). Of note, all results obtained were consistent after excluding SOTRs with recurrent infections (n = 32, 2.0%).

4. Discussion

This comprehensive and detailed analysis of nationwide prospective registry data provided valuable insights into the real-world experiences of Japanese COVID-19 SOTRs from the beginning to the final stages of the pandemic. To the best of our knowledge, this is the first study to present the SMR trends of COVID-19 in the SOTR population. The strength of the present

Table 1
Characteristics of study participants.

		Total (N = 1632)	Waves 1-3 (Beta) (N = 96)	Wave 4 (Alpha) (N = 75)	Wave 5 (Delta) (N = 124)	Wave 6 (Omicron BA.1/2) (N = 884)	Wave 7 (Omicron BA.5) (N = 453)	*P* value
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Transplant organ	Heart	20 (1)	2 (2)	1 (1)	3 (2)	10 (1)	4 (1)	.28
	Lungs	25 (2)	2 (2)	1 (1)	3 (2)	11 (1)	8 (2)	
	Liver	408 (25)	14 (15)	23 (31)	33 (27)	241 (27)	97 (21)	
	Kidneys	1170 (72)	77 (80)	50 (67)	84 (68)	616 (70)	343 (76)	
	Small intestine	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	
	Multiple organs	8 (0.5)	1 (1)	0 (0)	1 (1)	6 (1)	0 (0)	
Duration from transplantation (mo)	Median (IQR)	80 (38-145)	72 (36-143)	94.5 (48.5-181.5)	69.5 (31-143)	81 (40-146)	83 (37-141)	.21
Follow-up period (d)	Median (IQR)	125 (33-233)	606.5 (31-688)	497 (48-554)	380.5 (32-432)	167 (43.5-232)	70 (24-98)	<.01
Age (y)	Median (IQR)	48 (35-59)	49.5 (38.5-62.5)	52 (35-62)	50 (39.5-60)	47 (33-58)	48 (34-59)	.06
Sex	Male	1001 (61)	68 (71)	49 (65)	79 (64)	528 (60)	277 (61)	.25
Body mass index/ Laurel index/Kaup index	Underweight	193 (12)	12 (13)	5 (7)	16 (13)	110 (13)	50 (11)	.01
	Normal	915 (57)	48 (50)	40 (53)	72 (59)	471 (54)	284 (64)	
	Obese	510 (32)	36 (38)	30 (40)	35 (28)	297 (34)	112 (25)	
Smoking	Never	936 (69)	38 (51)	37 (61)	62 (60)	530 (72)	269 (70)	<.01
	Current/Former	419 (31)	37 (49)	24 (39)	42 (40)	203 (28)	113 (30)	
Underlying illnesses	Any	1055/1535 (69)	73/87 (84)	44/68 (65)	92/117 (79)	568/832 (68)	278/431 (65)	<.01
	Diabetes mellitus	362/1631 (22)	30 (31)	21 (28)	41 (33)	184/883 (21)	86 (19)	<.01
	Hypertension	617/1631 (56)	59 (61)	38 (51)	77 (62)	499 (56)	244/452 (54)	.32
	Cardiovascular diseases	114 (7)	7 (7)	5 (7)	12 (10)	60 (7)	30 (7)	.82
	Chronic respiratory diseases	37/1630 (2)	2/95 (2)	2 (3)	4/123 (3)	24 (3)	5 (1)	.38
	Chronic liver diseases	21/1630 (1)	8/95 (8)	0 (0)	2 (2)	8/883 (1)	3 (1)	<.01
	Chronic kidney diseases	30/1499 (2)	2/86 (2)	3/65 (5)	3/112 (3)	17/810 (2)	5/426 (1)	.39
	Cerebrovascular diseases	49 (3)	4 (4)	1 (1)	7 (6)	25 (3)	12 (3)	.35
	Malignant neoplasm	69 (4)	3 (3)	3 (4)	5 (4)	41 (5)	17 (4)	.92
HLA A24 typing	Yes	749 (59)	37 (53)	28 (51)	60 (59)	419 (60)	205 (58)	.55

(*continued on next page*)

Table 1 (*continued*)

		Total (N = 1632)	Waves 1-3 (Beta) (N = 96)	Wave 4 (Alpha) (N = 75)	Wave 5 (Delta) (N = 124)	Wave 6 (Omicron BA.1/2) (N = 884)	Wave 7 (Omicron BA.5) (N = 453)	*P* value
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Donor type	Deceased	161 (10)	11 (12)	8 (11)	19 (15)	87 (10)	36 (8)	.18
Acute rejection <3 months before COVID-19 diagnosis	Yes	11 (1)	0 (0)	1 (1)	2 (2)	5 (1)	3 (1)	.57
Calcineurin inhibitors	No	23 (1)	0 (0)	1 (1)	4 (3)	14 (2)	4 (1)	.11
	Tac	460 (28)	29 (31)	26 (35)	33 (27)	266 (30)	106 (23)	
	TacER	904 (55)	55 (58)	34 (45)	67 (54)	471 (53)	277 (61)	
	CsA	243 (15)	11 (12)	14 (19)	20 (16)	132 (15)	66 (15)	
Antimetabolites	No	301 (19)	15 (17)	11 (16)	22 (18)	166 (19)	87 (19)	.43
	MMF	1239 (77)	70 (78)	53 (78)	95 (79)	682 (78)	339 (75)	
	AZ	23 (1)	2 (2)	2 (3)	0 (0)	7 (1)	12 (3)	
	MZ	46 (3)	3 (3)	2 (3)	4 (3)	22 (3)	15 (3)	
mTOR inhibitors	No	1314 (81)	67 (72)	64 (85)	98 (80)	720 (82)	365 (81)	.16
	Yes	305 (19)	26 (28)	11 (15)	25 (20)	158 (18)	85 (19)	
Steroids	No	385 (24)	18 (20)	14 (19)	26 (21)	231 (26)	96 (21)	.02
	PSL	449 (28)	30 (33)	32 (44)	30 (24)	236 (27)	121 (27)	
	mPSL	781 (48)	44 (48)	26 (36)	67 (54)	411 (47)	233 (52)	
Combination of medications	None	5 (0.3)	0 (0)	0 (0)	1 (1)	3 (0.4)	1 (0.2)	.49
	1	170 (11)	4 (5)	4 (6)	10 (8)	101 (12)	51 (11)	
	2	217 (14)	12 (14)	14 (22)	17 (14)	125 (14)	49 (11)	
	3	1021 (65)	57 (67)	39 (60)	79 (66)	550 (64)	296 (66)	
	4	167 (11)	12 (14)	8 (12)	12 (10)	85 (10)	50 (11)	
Rituximab <6 mo before COVID-19 diagnosis	Yes	12 (1)	1 (1)	0 (0)	1 (1)	9 (1)	1 (1)	.5

(*continued on next page*)

Table 1 (*continued*)

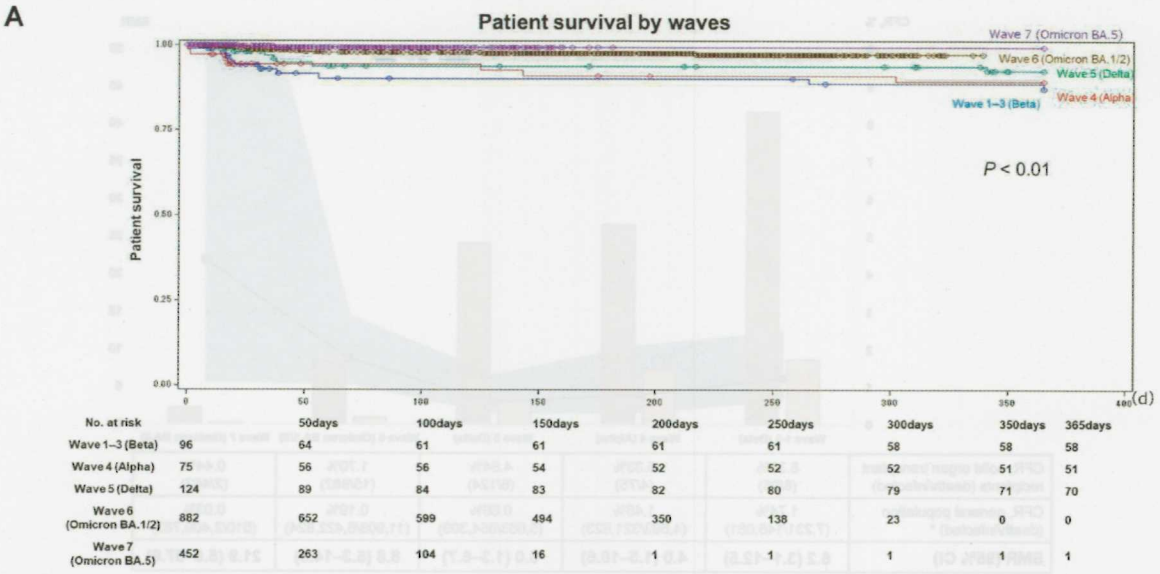
		Total (N = 1632) n (%)	Waves 1-3 (Beta) (N = 96) n (%)	Wave 4 (Alpha) (N = 75) n (%)	Wave 5 (Delta) (N = 124) n (%)	Wave 6 (Omicron BA.1/2) (N = 884) n (%)	Wave 7 (Omicron BA.5) (N = 453) n (%)	*P* value
Antithymoglobulin <3 mo before COVID-19 diagnosis	Yes	6 (0.4)	1 (1)	0 (0)	0 (0)	3 (0.3)	2 (0.4)	.73
Number of infections	1	1600 (98)	94 (98)	74 (99)	123 (99)	866 (98)	443 (98)	.89
	2	31 (2)	2 (2)	1 (1)	1 (1)	18 (2)	9 (2)	
	3	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	
Vaccination before infection	No	420 (29)	96 (100)	50 (88)	54 (49)	157 (20)	63 (16)	<.01
	Yes	1004 (71)	0 (0)	7 (12)	57 (51)	615 (80)	325 (84)	
Number of vaccinations	1	35 (4)		2 (33)	19 (35)	12 (2)	2 (1)	<.01
	2	486 (52)		2 (33)	35 (64)	377 (66)	72 (23)	
	3	394 (42)		2 (33)	1 (2)	182 (32)	209 (68)	
	4	26 (3)		0 (0)	0 (0)	2 (0.4)	24 (8)	
Period from onset to diagnosis (d)	Four days or longer	150 (13)	25 (40)	15 (25)	18 (19)	69 (12)	23 (7)	<.01
Symptoms at diagnosis	Yes	1479 (92)	88 (93)	66 (88)	116 (96)	793 (92)	416 (93)	.32

AZ, azathioprine; COVID-19, coronavirus disease 2019; CsA, cyclosporine; HLA, human leukocyte antigen; IQR, interquartile range; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; mPSL, methylprednisolone; MZ, mizoribine; PSL, prednisolone; Tac, tacrolimus; TacER, tacrolimus extended-release.

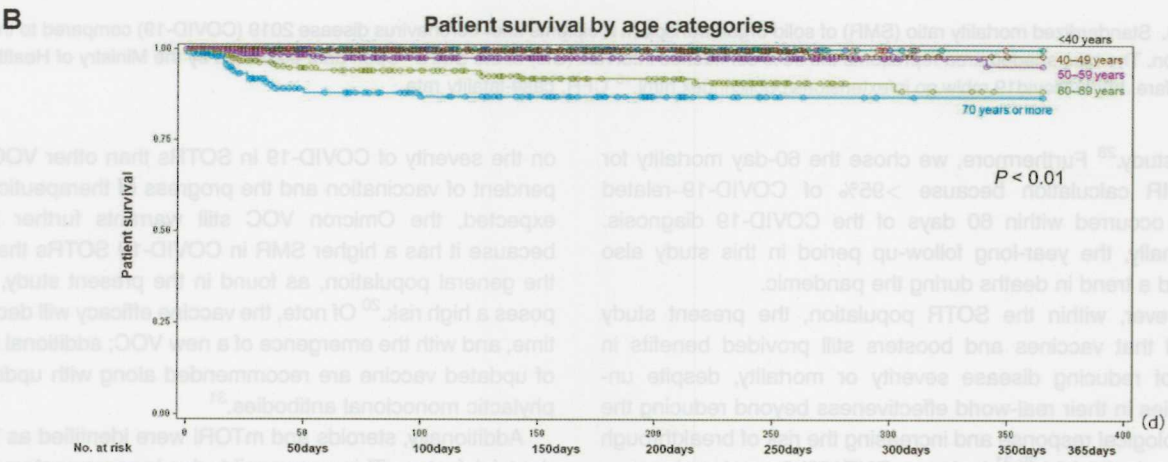
Table 2
Major outcomes of study participants.

		Total (N = 1632)	Waves 1-3 (Beta) (N = 96)	Wave 4 (Alpha) (N = 75)	Wave 5 (Delta) (N = 124)	Wave 6 (Omicron BA.1/2) (N = 884)	Wave 7 (Omicron BA.5) (N = 453)	*P* value
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Hospital admission		808 (50)	88 (92)	63 (85)	105 (85)	415 (47)	137 (31)	<.01
ICU admission		63 (5)	14 (21)	10 (20)	11 (11)	23 (3)	5 (1)	<.01
Pneumonia		338 (22)	47 (52)	30 (43)	57 (48)	152 (19)	52 (12)	<.01
Oxygen demand		220 (14)	38 (41)	31 (44)	40 (35)	82 (10)	29 (7)	<.01
Nasal cannula or mask		150 (10)	24 (23)	23 (33)	29 (26)	53 (6)	21 (5)	<.01
High-flow nasal cannula		39 (3)	3 (4)	5 (8)	8 (7)	18 (2)	5 (1)	<.01
NPPV		5 (0.3)	0 (0)	0 (0)	2 (2)	0 (0)	3 (0.7)	.02
Mechanical ventilation		49 (3)	12 (14)	5 (8)	8 (7)	19 (2)	5 (1)	<.01
ECMO		5 (0.3)	1 (1)	1 (2)	2 (2)	1 (0.1)	0 (0)	<.01
Graft loss		14 (0.9)	2 (2)	0 (0)	1 (1)	9 (1)	2 (0.5)	.45
Severity	Mild	1,214 (77)	37 (39)	26 (35)	53 (45)	707 (82)	391 (89)	<.01
	Moderate	283 (18)	40 (42)	35 (47)	52 (44)	114 (13)	42 (10)	
	Severe (including death)	89 (6)	18 (19)	13 (18)	13 (11)	37 (4)	8 (2)	
Prognosis	Death	44 (3)	10 (10)	7 (9)	7 (6)	18 (2)	2 (0.4)	<.01
	Death within 30 d	22 (1)	5 (5)	4 (5)	2 (2)	10 (1)	1 (0.2)	<.01
	Death within 60 d	35 (2)	8 (8)	4 (5)	6 (5)	15 (2)	2 (0.4)	<.01
	Death within 180 d	39 (2)	8 (8)	6 (8)	6 (5)	17 (2)	2 (0.4)	<.01
	Death within 1 y	43 (3)	9 (9)	7 (9)	7 (6)	18 (2)	2 (0.4)	<.01

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; NPPV, noninvasive positive pressure ventilation.



No. at risk		50days	100days	150days	200days	250days	300days	350days	365days
Wave 1–3 (Beta)	96	64	61	61	61	61	58	58	58
Wave 4 (Alpha)	75	56	56	56	54	52	52	51	51
Wave 5 (Delta)	124	89	84	83	82	80	79	71	70
Wave 6 (Omicron BA.1/2)	882	652	599	494	350	138	23	0	0
Wave 7 (Omicron BA.5)	452	263	104	16	1	1	1	1	1



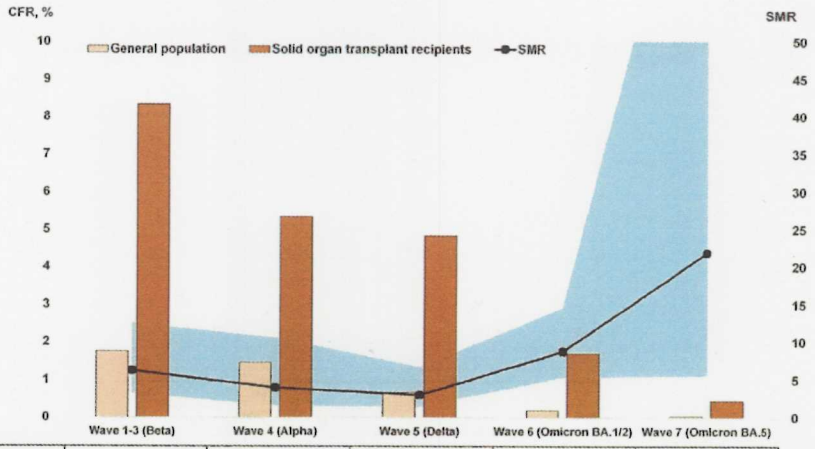
No. at risk		50days	100days	150days	200days	250days	300days	350days	365days
<20 years	190	127	85	61	40	14	8	6	6
20–29 years	141	106	86	70	52	37	23	20	20
30–39 years	188	132	108	88	68	41	28	25	25
40–49 years	349	236	193	159	124	77	46	37	36
50–59 years	363	261	214	161	129	81	49	41	41
60–69 years	249	169	142	111	97	61	44	38	38
70 years or more	149	93	75	58	36	21	15	14	14

Figure 2. Patient survival categorized by (A) wave and (B) age categories. *P* value for the log-rank test.

study lies in the homogenous population of Japanese SOTRs, who generally have universal insurance and immunosuppression regimens and demonstrate strict compliance (87.1%–94.4%) with the safety measures or therapeutics published by the JST COVID-19 guidelines.[6] Consequently, this minimized the possible impact of unexpected confounders.

In the present study, we observed that disease severity and mortality rates decreased over time, particularly after the Omicron era, which is consistent with the findings of the general population.[19] However, the case-fatality rates for severe disease and SMR were consistently high, despite the availability of vaccines and booster shots in the late phase of the pandemic.[20] Specifically, in the present study, SMR showed a U-shaped pattern, with a nadir in the Delta era followed by a subsequent increase thereafter.

The suboptimal immune response to vaccines and boosters in SOTRs compared to the general population could explain this widened SMR gap toward the Omicron era.[21-25] We speculated that the original vaccines were effective until the Delta era but their efficacy declined drastically, which led to increased breakthrough infection in the Omicron era.[25,26] This phenomenon might also apply to future pandemics. A multicenter study from Spain conducted from February 28, 2020, to April 7, 2020, with an observation period of 23 days (median), revealed a low SMR of 0.96 (95% CI: 0.94-0.97, converted from the percent expression) in 111 liver transplant recipients compared to that in the general population.[27] Although the author concluded that this was possibly due to the protective effect of chronic immunosuppression on COVID-19 exacerbation, this has now been refuted and was regarded as a risk in a recent meta-analysis and



	Wave 1-3 (Beta)	Wave 4 (Alpha)	Wave 5 (Delta)	Wave 6 (Omicron BA.1/2)	Wave 7 (Omicron BA.5)
CFR, solid organ transplant recipients (death/infected)	8.33% (8/96)	5.33% (4/75)	4.84% (6/124)	1.70% (15/882)	0.44% (2/452)
CFR, general population (death/infected) *	1.74% (7,231/146,081)	1.46% (4,693/321,823)	0.66% (5,663/854,309)	0.19% (11,908/6,422,824)	0.03% (610/2,409,783)
SMR (95% CI)	**6.2 (3.1–12.5)**	**4.0 (1.5–10.6)**	**3.0 (1.3–6.7)**	**8.8 (5.3–14.5)**	**21.9 (5.5–87.6)**

Figure 3. Standardized mortality ratio (SMR) of solid organ transplant recipients after coronavirus disease 2019 (COVID-19) compared to the general population. The blue shaded area represents the 95% confidence intervals (CIs) of the SMR. *Open data published by the Ministry of Health, Labour, and Welfare. https://covid19.mhlw.go.jp/extensions/public/index.html.[15] CFR, case-fatality rate.

in this study.[28] Furthermore, we chose the 60-day mortality for the SMR calculation because >95% of COVID-19–related deaths occurred within 60 days of the COVID-19 diagnosis. Additionally, the year-long follow-up period in this study also revealed a trend in deaths during the pandemic.

However, within the SOTR population, the present study showed that vaccines and boosters still provided benefits in terms of reducing disease severity or mortality, despite uncertainties in their real-world effectiveness beyond reducing the immunological response and increasing the risk of breakthrough infections by 82-fold.[29-31] In Japan, BNT162b2 vaccines became available since February 17, 2021, just before the beginning of the Alpha era, followed by mRNA1273 and ChAdOx1 nCoV-19 on May 23, 2021, and August 16, 2021, respectively, though the vaccine most administered was BNT162b2 followed by mRNA1273.[12] As of July 31, 2022 (the end of enrolment of this study), the first, second, and third doses were completed in 77.4%, 76.9%, and 63.7% of cases, respectively.[32] Over 50% of cases in the Delta era received the vaccine, and there is universal access to additional booster shots, provided every 3 months by the government, which resulted in >80% vaccination coverage during the Omicron era in the present study. Consequently, this may have contributed to the low mortality rates observed in Japanese SOTRs. A study from Colombia revealed the benefits of full vaccination and boosters on prevention, hospitalization, and death in SOTRs. However, it did not specify the baseline immunosuppression or transplanted organs.[29] Our study confirmed the independent impact of vaccinations in reducing disease severity and mortality.

Moreover, this study makes a novel contribution to the existing literature by directly comparing the VOCs across the pandemic and revealing that the Omicron VOC had a more favorable impact on the severity of COVID-19 in SOTRs than other VOCs, independent of vaccination and the progress of therapeutics.[3,33] As expected, the Omicron VOC still warrants further attention because it has a higher SMR in COVID-19 SOTRs than that in the general population, as found in the present study, and still poses a high risk.[20] Of note, the vaccine efficacy will decline over time, and with the emergence of a new VOC; additional boosters of updated vaccine are recommended along with updated prophylactic monoclonal antibodies.[31]

Additionally, steroids and mTORi were identified as independent risk factors. This was possibly due to some centers adopting 4 immunosuppressive drug regimens to avoid rejection and anti-HLA antibodies, which may induce overimmunosuppression that could have been avoided during the COVID-19 pandemic.[34] Moreover, the present study did not find any considerable differences in disease severity and mortality rates among different transplanted organs, which may be attributed to the relatively small sample size of lung transplant recipients and lower overall mortality rates than those reported in other studies.[2,33,35] Other risk factors, including older age and underlying illnesses, were in line with the previous studies.[2,33]

The potential impact of immunosuppression adjustment on COVID-19 and other infections remains to be fully elucidated.[3] In a previous meta-analysis, adjustments were made in 76.2% and 38.7% of cases for antimetabolites and calcineurin inhibitors, respectively, resulting in a 1.0% incidence of acute rejection, which is in line with our data.[36] The present study could not definitively establish the benefits of immunosuppression adjustment because the disease severity was retrospectively assigned to the highest degree. However, because disease severity requiring withdrawal of immunosuppression would evoke immunological damage to allografts, attention should be focused on

Table 3
Independent risk and protective factors for moderate or severe COVID-19 or deaths per multivariate analysis.

		Outcome incidence (N = 1586[a])	Multivariate model	
		n/N (%)	OR (95% CI)	*P* value
Wave	1–3 (Beta)	58/95 (61)	1.00	
	4 (Alpha)	48/74 (65)	1.65 (0.59-4.57)	.34
	5 (Delta)	65/118 (55)	1.22 (0.50-2.95)	.66
	6 (Omicron BA.1/2)	151/858 (18)	0.23 (0.10-0.52)	<.01
	7 (Omicron BA.5)	50/441 (11)	0.11 (0.05-0.28)	<.01
Age (y)	<20	4/178 (2)	0.1 (0.02-0.50)	<.01
	20-29	22/135 (16)	0.93 (0.42-2.04)	.85
	30-39	33/186 (18)	0.8 (0.42-1.50)	.48
	40-49	74/344 (22)	1.00	
	50-59	87/359 (24)	0.84 (0.51-1.38)	.49
	60-69	93/242 (38)	1.96 (1.15-3.34)	.01
	70+	59/142 (42)	2.61 (1.40-4.86)	<.01
			(Trend $P < .01$)	
Underlying illnesses	No	45/467 (10)	1.00	
	Yes	315/1029 (31)	2.33 (1.37-3.97)	<.01
mTOR inhibitors	No	275/1273 (22)	1.00	
	Yes	91/300 (30)	1.67 (1.06-2.64)	.03
Steroids	No	39/367 (11)	1.00	
	PSL/mPSL	322/1202 (27)	2.4 (1.24-4.63)	<.01
Antithymoglobulin <3 mo before COVID-19 diagnosis	No	363/1571 (23)	1.00	
	Yes	5/6 (83)	23.47 (2.07-265.92)	.01
Vaccination before infection	No	146/409 (36)	1.00	
	Yes	189/984 (19)	0.46 (0.28-0.76)	<.01
Number of vaccinations	0	146/409 (36)	1	
	1-2	120/412 (23)	0.49 (0.29-0.84)	<.01
	3-4	59/412 (14)	0.29 (0.15-0.55)	<.01
			(Trend $P < .01$)	

Logistic regression model.
The multivariate model included variables associated significantly with disease severity in univariate analysis ($P < .05$). Details are available in Supplementary Table S4.
CI, confidence interval; COVID-19, coronavirus disease 2019; mTOR, mammalian target of rapamycin; mPSL, methylprednisolone; OR, odds ratio; PSL, prednisolone.
[a] Forty-six participants without disease severity and outcome status were excluded.

reducing the risk of severe disease.[37] Trends in therapeutics suggest that remdesivir and molnupiravir remain the gold standards for treating inpatient and outpatient SOTRs, respectively.

Long COVID is a multimodal disease occurring in 10% of the global population (>65 million cases). The incidence is increased in severe cases: 50%–70%, 10%–30%, and 10%–12% in hospitalized, nonhospitalized, and vaccinated cases, respectively.[38] Evidence regarding long COVID in SOTRs is limited. A recent prospective study via phone survey including 780 kidney transplant recipients with a prior COVID-19 infection revealed that 27% had experienced long COVID and 17% had been unable to return to work within 3 months.[39] The risk of long COVID was related to the number of symptoms, similar to that in the general population.[38,39] The reported incidence of long COVID was much lower (3%) in this study, reflecting a difference in the perspectives of the respondents. However, the decline in long COVID prevalence over time was in line with the previous study, possibly reflecting the intensity of acute illness.[39] Further follow-up is warranted.

The limitations of this study include its retrospective assignment of the disease severity, which was defined as the highest degree during the disease course, as the initial grading was not collected in this study. Because this registry was designated only for COVID-19–positive SOTRs, we could not analyze whether

Table 4
Independent risk factors for mortality within 60 days of COVID-19 diagnosis.

		n/Observation periods (Person-months)	Mortality rate per 1000 person-months	Multivariate model HR (95% CI)	*P* value
Total (N = 1629[a])		35/2578.3	13.57		
Wave	1-3	8/151.8	52.70	1.00	
	4	4/124.6	32.10	0.63 (0.12-3.37)	.59
	5	6/198.0	30.30	0.86 (0.19-3.94)	.85
	6	15/1444.6	10.38	0.25 (0.05-1.39)	.11
	7	2/659.4	3.03	0.05 (0.00-0.55)	.02
Age (y)	<20	0/315.4	0.00	NA	
	20-29	0/238.4	0.00	NA	
	30-39	0/293.2	0.00	NA	
	40-49	1/536.0	1.87	1.00	
	50-59	7/579.4	12.08	4.48 (0.52-38.60)	.17
	60-69	12/389.8	30.79	10.65 (1.32-86.07)	.03
	70+	15/226.1	66.34	24.34 (3.06-193.42)	<.01
				(Trend $P < .01$)	

Cox proportional hazard model.
The multivariate model included variables associated significantly with death within 60 days in univariate analysis ($P < .05$). Details are available in Supplementary Table S5.
CI, confidence interval; COVID-19, coronavirus disease 2019; NA, not applicable; OR, odds ratio.
[a] Three participants without outcome status were excluded.

SMR was higher in the COVID-positive subgroup than comparing COVID-19-negative SOTRs to the COVID-19–negative general population, as well as SMR for SOTRs prior to the COVID-19 pandemic. We have collected data from the transplant centers on whether SOTRs were initially treated at transplant centers or at different institutions. There is a possibility that some data from different institutions might have been missing. Although the number of nonabdominal SOT programs is low, the majority of the nonabdominal SOTs were performed in the participating programs. Therefore, the results of this study sufficiently represent the national trend for COVID-19–affected nonabdominal SOTRs.

Regarding the observation period, patient enrolment ended in July 2022, in the middle of Wave 7 (Omicron BA.5), and the Japanese government stopped tracking all COVID-19 cases in September 2022, 2 months after the completion of the study. Thus, the SMR calculated in this study is based on accurate statistics and the maximum observation period available in our patient cohort. The standardized incidence ratio was difficult to calculate from the present study. However, the prevalence of confirmed cases was 7.3% in SOTRs in the present study, whereas it was 10.2% (calculated from open data as of July 31, 2023) in the general population.[15] The reason for the discrepancy in the data might be explained by the recommendation of self-quarantine by the transplant societies, including JST, after the COVID-19 pandemic.[6] Although the evidence was scarce on whether transplant recipients were more likely to seek testing and care in COVID-19, a study from Finland on seasonal influenza before the COVID-19 era revealed that the risk of laboratory-confirmed influenza was significantly higher among kidney transplant recipients than the general population, possibly due to lower threshold for acquiring laboratory testing in transplanted patients.[40] Because accurate data on the type of vaccine were not available, we were unable to investigate whether the difference in vaccine affected outcomes. Because the Japanese open data for COVID-19 mortality rates in the general population are only available for the overall case-fatality rate, comparing the granular mortality rates, such as at 30, 60, 180, and 365 days after diagnosis, was difficult in the present study. The demographic data for the general population stem from confirmed COVID-19 daily cases and deaths recorded in the HER-SYS in Japan.[15] Unfortunately, the HER-SYS only records simple outcomes and lacks detailed baseline data (such as diabetes and immunosuppression) beyond age and sex. Thus, tracking individual outcomes in the general population across the waves was difficult. Furthermore, our registry of transplant recipients may be encompassed within this general population reference for SMR analysis. However, alongside SOTRs,[27] individuals with immunosuppressed conditions such as autoimmune rheumatic diseases, inflammatory bowel diseases, and hematopoietic stem cell transplantation may be included.[41-43] These limitations of the SMR analysis, consistent with other reports, were disregarded due to the substantial disparity between the number of COVID-19–affected SOTRs and that of COVID-19 in the general population.[27,41-43] The generalization of the results of this study in another geographical setting may be difficult due to genetic differences, overall risk factors such as obesity, and management

of SOTRs during the COVID-19 pandemic. In the early phase of the pandemic, there were insufficient supplies of remdesivir, and hospital admission itself was difficult because of the exponential increase of COVID-19 patients. Thus, various nonauthorized drugs, such as favipiravir and ivermectin, were used globally for outpatients as there was no choice at that time, which may have affected the outcomes of COVID-19–positive SOTRs.

Conclusively, in this large-scale national registry study, we showed the epidemiology of the real-world experience in Japan, including the efficacy of vaccines, risk factors of moderate/severe disease, including older age and intense immunosuppression, and the consistently higher mortality risk than that in the general population, even in the final phase of the pandemic. Therefore, SOTRs need to undergo protective measures and receive additional booster shots to mitigate the risk of moderate/severe disease and death.

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A completed STROBE statement checklist for cohort studies is provided in Supplementary Table S6.

Author contributions

Concept and design: S.Y., K.S., M.Y., Y.N., T.H., K.Y., H.E.
Data curation: S.Y., K.S.
Analysis and interpretation of data: S.Y., K.S., S.O., M.Y., Y.N., T.H., K.Y., H.E.
Drafting of the manuscript: S.Y., S.O., T.H.
Critical revision of the manuscript for important intellectual content: S.Y., K.S., M.Y., Y.N., T.H., K.Y., H.E.
Direct access to the data: S.Y., K.S., S.O., T.H., H.E.
Statistical analysis: S.O.
Obtained funding: H.E.

Data availability

The data are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2024.03.016.

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周術期トリプルネガティブ乳癌に対する免疫チェックポイント阻害剤の使用経験

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【はじめに】

Pembrolizumab（キイトルーダ®）は，ヒト化抗ヒトPD-1モノクローナル抗体で免疫チェックポイント阻害剤（Immuno Checkpoint Inhibitor：以下ICI）の一つである。2022年9月に新たに「ホルモン受容体陰性かつHER2陰性（トリプルネガティブ）で再発高リスクの乳癌における術前・術後薬物療法」として適応が承認された[1]。

当院では，これまでトリプルネガティブ乳癌（Triple Negative Breast Cancer：TNBC）9症例に対してICIの投与を行なっており，その中で高い治療効果が得られた1例を経験したので報告する。

【症例】

40歳代の女性，20XX年に左乳房の疼痛としこりを主訴に前医を受診。乳房超音波検査で左乳房に2cm大の腫瘤を認め，針生検で浸潤性乳癌［充実型 ER; J-score 0, PgR; J-score 0, HER2; Score 0］と診断され，当院を紹介受診した。

身体所見：左乳房頭側に3cm大の弾性硬腫瘤を触知
家族歴：叔母乳癌
既往歴：アレルギー性鼻炎，その他特記すべき事項なし
検診歴：2年前は異常なし

【検査所見】

血液生化学検査：
腫瘍マーカー正常値，その他特記すべき所見なし

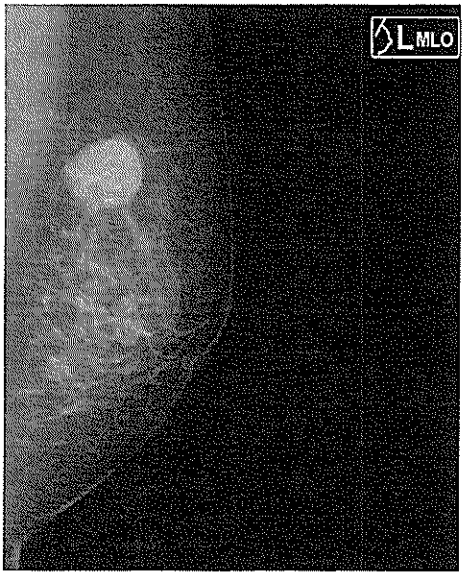

Fig. 1　初診時マンモグラフィ
微細鋸歯状高濃度腫瘤あり。カテゴリー4。

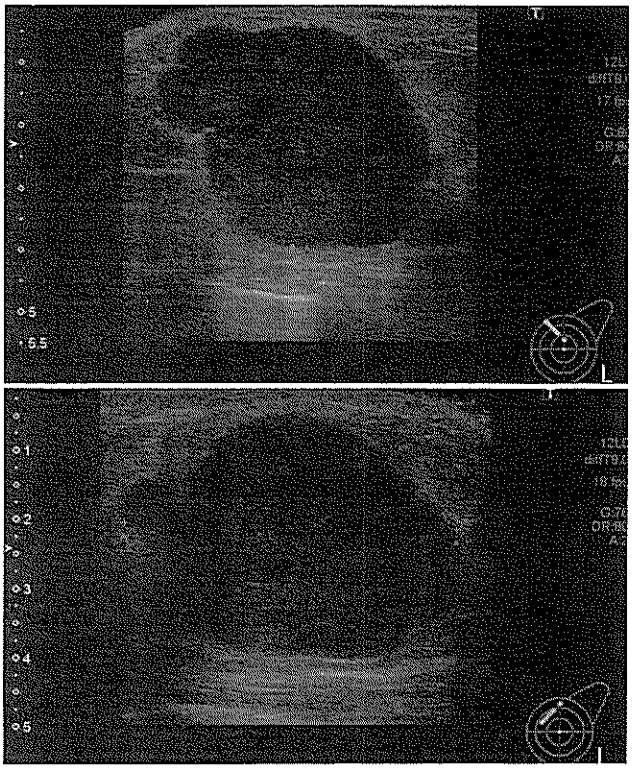

Fig. 2　初診時乳房超音波検査
左乳房11時Mに46x36x42mmの分葉形の低エコー腫瘤を認めた。

マンモグラフィ：
左MLO-Uに微細鋸歯状高濃度腫瘤を認める（Fig. 1）。
乳房超音波検査：
左乳房上内側部に46x36x42mmの分葉形の低エコー腫瘤を認め，境界明瞭粗造，内部エコー不均一，後方エコー増強，辺縁及び周囲に拍動性血流シグナルあり（Fig. 2）。
全身CT検査：
左乳房頭側に44mmの充実性腫瘤あり（Fig. 3-1）。左腋窩リンパ節腫大を認めるが明らかな遠隔転移なし（Fig. 3-2）。
乳房MRI検査：
左乳房上部に48mm大の不整形腫瘤あり（Fig. 4）。
BRCA 1/2 遺伝子検査：陰性

【臨床病期】
cT2N1M0, StageIIB

【治療方針】
① Pembrolizumab（以下，PEM）200mgを3週間隔（Q3W，21日を1サイクル），Paclitaxel（以下，PTX）80mg/m^{2}を1週間間隔（QW，21日を1サイクル），Carboplatin（以下，CBDCA）AUC5に相当する量をQ3Wで4サイクル点滴静注する。
② PEM200mgをQ3W，Epirubicin Hydrochloride 390mg/m^{2}をQ3W，Cyclophosphamide（以下，CPA）600mg/m^2（無水物換算）をQ3Wで4サイクル（以下，EC）点滴静注する。
③ ①②終了後に，乳癌根治手術を行う。
④ 手術後に，PEM200mgをQ3Wで9サイクル点滴静注する（Table. 1）。

【治療経過】
20XX年より，PEM + PTX + CBDCAを開始。副作用により末梢神経障害や脱毛，軽度の頭痛，嘔気を認めるも，大きな有害事象なく4サイクルを終了した。経過中はICIによる明らかな免疫関連副作用（immune-related Adverse

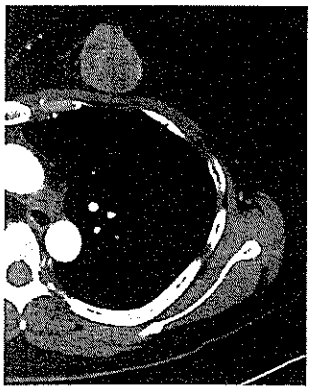
Fig. 3 - 1

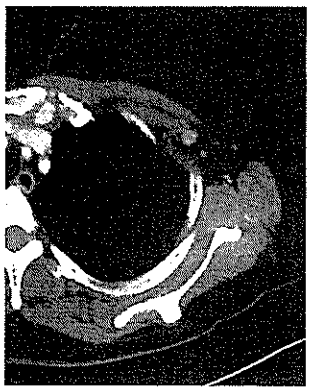
Fig. 3 - 2

治療開始前の造影CT
左乳房上内側部に44mmの充実性腫瘤を認めた。左腋窩リンパ節レベルⅠの腫大を認めた。

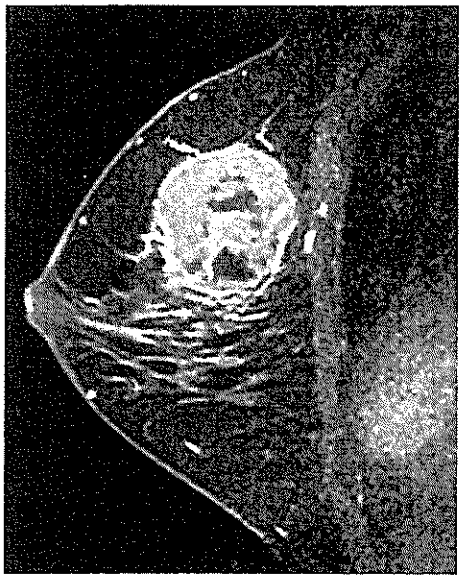
Fig. 4 治療開始前の乳房造影MRI，
左乳房上部に48mm大の不整形腫瘤を認めた。

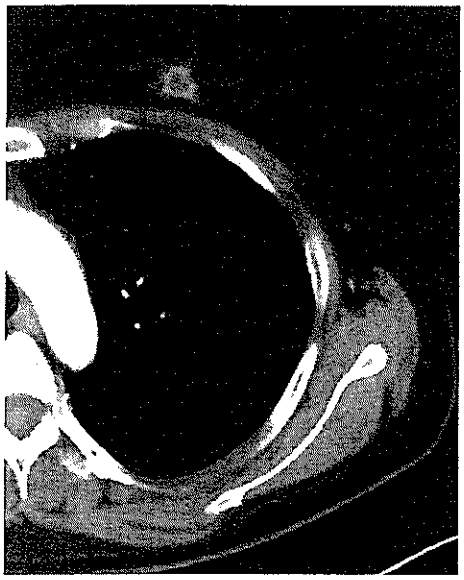
Fig. 5
Pembrolizumab + PTX +CBDCA 4コース終了後の造影CT
腫瘍の縮小を認めた。

Events：irAE）は認められなかった。投与後の治療効果判定のCTでは，腫瘍の縮小が認められた（Fig. 5）。

続いて，PEM＋ECを開始。1サイクル開始後，感染性鼻炎とGrade 3の貧血，血小板減少を認め，輸血を行なった。

2サイクルと4サイクル後には感染性の肺炎を併発し，3サイクル目には発熱性好中球減少症を来した。

PEM＋ECによる治療中には，サイクル毎に様々な合併症が認められた。毎回irAEとの鑑別を要することとなったが，全体を通して明らかなirAEは認められなかった。投与スケジュールの延期はあったが，手術前に一連の術前薬物治療を終えることができた。

PEM＋EC後のCTでは，腫瘍，腋窩リンパ節ともにさらに縮小が認められた（Fig. 6）。病期はycT1cN0M0:stageIと診断した。

初回治療開始から8ヶ月後に，乳癌根治術（左乳房全切除術＋センチネルリンパ節生検）を施行した。術後経過は良好で，第4病日に退院した。

病理診断は，病理学的完全奏効（pathological Complete Response：pCR）であった。病変部には炎症細胞浸潤や繊維化，ヘモジデリン沈着を認めるのみで癌細胞の明らかな残存は無く，摘出したリンパ節にも転移は認められなかった（Fig. 7）。

手術7か月後の現在までPEMを副作用なく継続中である。

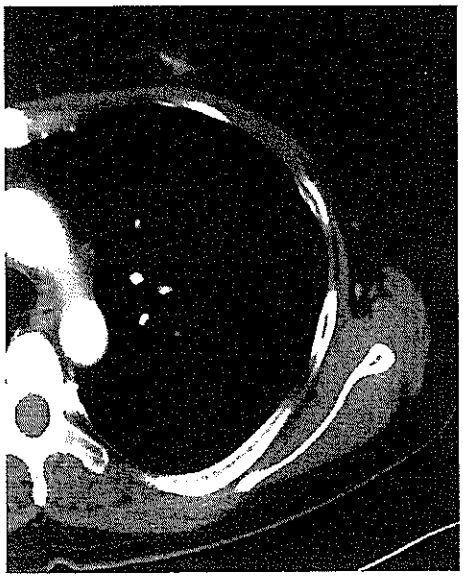

Fig. 6　Pembrolizumab＋EC 4コース終了後の造影CT
腫瘍の著明な縮小を認めた。

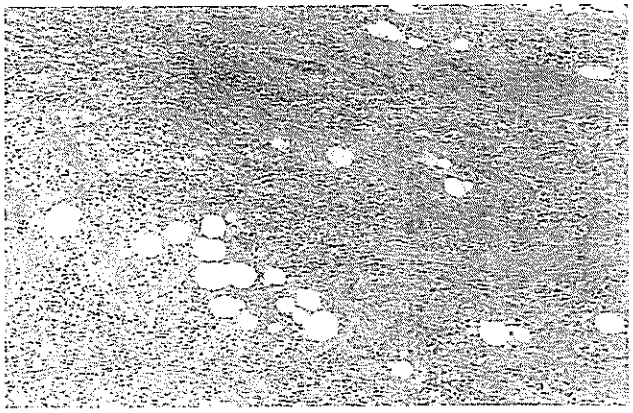

Fig. 7　手術検体の病理画像（x100倍）
病変部は炎症細胞浸潤や繊維化，ヘモジデリン沈着を認めるのみで癌細胞の明らかな残存は認められなかった。

【考察】

KEYNOTE-522試験においてpCR率は，PEM（キイトルーダ®）群で64.8%（95%CI：59.9, 69.5），プラセボ群で51.2%（95%CI：44.1, 58.3）であり，PEM（キイトルーダ®）群はプラセボ群に対してpCR率を有意に改善した[2]（推定群間差：13.6%，95%CI：5.4, 21.8，p＝0.00055，層別Miettinen and Nurminen法［片側］，有意水準α＝0.003）。当院では2024年1月時点まで，術前薬物療法としてPEMの使用を本症例含め9例経験している（Table. 2）。PEM使用9例中5例に手術を実施し，3例が病理学的完全奏功であった（pCR率: 60%）。その高い治療効果を確認することができた。

一方で，ICIの併用によりirAEや化学療法による有害事象の増加を認めたと報告されている（Table. 3）。本症例では，術前薬物療法中，特にPEM＋EC投与中に副作用を多岐に認めその都度irAEとの鑑別を要した。幸い投与中止に至らず，術前治療を完了することができた。

PEM使用９例中３例に，irAEとして甲状腺機能低下症と副腎皮質機能低下症を認め，全例ホルモン補充療法を行なっている。また直腸炎による投与中止を１例認めた。ICIの併用によりこれまで経験したことのない副作用が出現し得るので注意が必要である。

【結語】

周術期TNBCに対しICIを使用し，副作用により治療に難渋したが，良好な治療効果を得られた一例を経験した。

PEMの治療効果は高く，十分にirAEへの対策を整えたうえで，引き続き適応症例に使用していく方針である。

本検討は，第253回茨城外科学会において「周術期トリプルネガティブ乳癌に免疫チェックポイント阻害剤を投与した一例」として発表した。

【参考文献】

(1) 『乳癌診療ガイドライン2022年版　薬物療法CQ16』

(2) Schmid P,.et al; Pembrolizumab for early triple-negative breast cancer. N Engl J Med.2020;382（９）:810-21

Table. 1　投与スケジュール

	1サイクル			2サイクル			3サイクル			4サイクル		
	1週	2週	3週	4週	5週	6週	7週	8週	9週	10週	11週	12週
キイトルーダ	○			○			○			○		
パクリタキセル	○	○	○	○	○	○	○	○	○	○	○	○
カルボプラチン	○	○	○	○	○	○	○	○	○	○	○	○

	5サイクル			6サイクル			7サイクル			8サイクル		
	13週	14週	15週	16週	17週	18週	19週	20週	21週	22週	23週	24週
キイトルーダ	○			○			○			○		
エピルビシン	○	○	○	○	○	○	○	○	○	○	○	○
シクロフォスファミド	○	○	○	○	○	○	○	○	○	○	○	○

	1サイクル			2サイクル			3サイクル			4サイクル		
	1週	2週	3週	4週	5週	6週	7週	8週	9週	10週	11週	12週
キイトルーダ	○			○			○			○		

	5サイクル			6サイクル			7サイクル			8サイクル		
	13週	14週	15週	16週	17週	18週	19週	20週	21週	22週	23週	24週
キイトルーダ	○			○			○			○		

	9サイクル		
	25週	26週	27週
キイトルーダ	○		

Table. 2　当院のPembrolizumab投与例一覧（2024年１月時）

	年齢	ステージ	腫瘍径（mm）	手術	治療効果	術後治療	irAE
症例１	40歳代	IIB	44	実施	pCR	PEM継続	
症例２	40歳代	IIA	40	実施	SD	PEM継続	甲状腺機能低下 副腎皮質機能低下
症例３	40歳代	IIIB	42	実施	pCR	PEM継続	
症例４	60歳代	IIB	34	実施	SD		甲状腺機能低下 副腎皮質機能低下
症例５	60歳代	IIA	28	実施	pCR	PEM継続	甲状腺機能低下 副腎皮質機能低下
症例６	50歳代	IIA	21	未実施	(cCR)		
症例７	40歳代	IIB	26	未実施	(cCR)		
症例８	50歳代	IIA	27	未実施	(cPR)		直腸炎（投与中止）
症例９	40歳代	IIA	22	未実施	(cCR)		

PEM：Pembrolizumab
症例１が本症例

Table. 3 - 1　併合期（術前薬物療法期及び術後薬物療法期）の主な副作用

	キイトルーダ群		プラセボ群	
	全Grade	Grade３以上	全Grade	Grade３以上
副作用発現例	98.9%	77.1%	99.7%	73.3%
悪　心	63.2%	3.4%	63.0%	1.5%
脱毛症	60.2%	0	56.6%	0
貧　血	54.8%	18.0%	55.3%	14.9%
好中球数減少	46.9%	34.5%	47.6%	33.4%
疲　労	42.1%	3.6%	38.8%	1.5%
下　痢	30.4%	2.6%	25.2%	2.3%
発熱性好中球減少症	18.4%	17.8%	16.7%	15.9%
発　熱	17.6%	1.0%	10.5%	0
血小板減少症	13.3%	2.7%	16.7%	2.8%
粘膜の炎症	13.2%	1.0%	11.6%	0.8%
鼻出血	9.7%	0	10.5%	0

Table. 3 - 2　併合期における主な免疫関連副作用

	キイトルーダ群		プラセボ群	
	全Grade	Grade３以上	全Grade	Grade３以上
甲状腺機能低下症	15.1%	0.5%	5.7%	0%
副腎機能不全	2.6%	1.0%	0	0
大腸炎	1.7%	0.8%	0.8%	0.3%

GradeはCTCAE v4.0
第4回中間解析，データカットオフ日：2021年３月23日より一部抜粋

Major Histocompatibility Complex 2023; 30 (3): 133-140

令和5年度　認定HLA　検査技術者認定制度試験問題に関する報告

令和5年度　認定HLA　検査技術者認定制度試験問題に関する報告

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土屋　尚之[7]・西村　泰治[8]・村田　誠[9]・湯沢　賢治[10]

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はじめに

日本組織適合性学会 のHLA 検査技術者・組織適合性指導者認定制度　第18回認定制度試験を，令和5年9月17日（日）に実施した。ここ数年は新型コロナウイルス（COVID-19）感染拡大の影響により，認定試験については本試験のみ実施し模擬試験を中止としてきたが，本年度は第31回大会が現地開催となったことで3年ぶりの模擬試験を開催した。模擬試験中止の間の措置として，ここ数年の難問解説は本試験での回答率を考慮して行ってきたが，今回は従来形に戻り模擬試験での正答率の低い，いわゆる“難問“について解説を行う。

なお，令和5年度の試験問題と正解は，学会ホームページ（https://jshi.smoosy.atlas.jp/ja/ninteikakomon）に掲載しているので参照されたい。

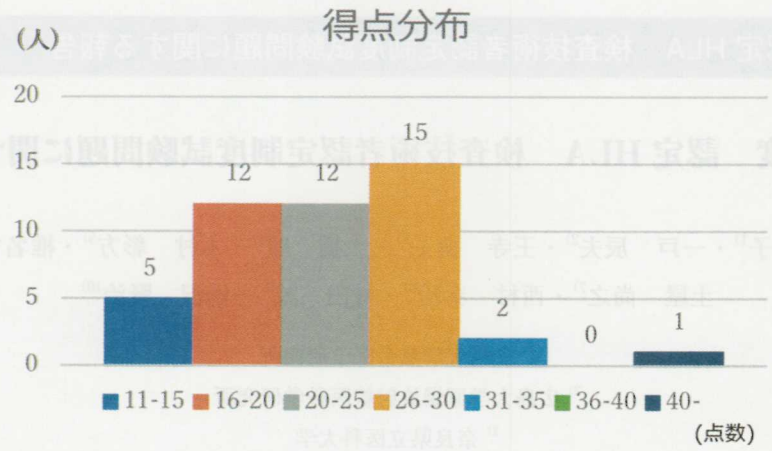
認定制度試験概要

令和5年度の日本組織適合性学会HLA 検査技術者・組織適合性指導者認定制度認定制度試験は第31回日本組織適合性学会大会中に，大会会場の一橋大学総合学術センター中会議場にて実施した。また，同時間帯に同5階第一会場において同一問題を利用して模擬試験（受験者47名）を実施した。

模擬試験受験者の内訳（回答分のみ）は，本学会員46名，非学会員1名，認定資格については，認定検査技術者19名，認定組織適合性指導者4名であった。受験者数は前回参加者数の半分余りと，オンライン併用開催の影響が考えられるものの，認定有資格者数は例年より増加していた。また，HLA 業務従事歴は，5年未満が25名，5年以上10年以下が4名，それ以上が18名であった。

試験問題は全50問で50点満点とし，模擬試験の点数分布は右図に示す通り，平均22.9点，標準偏差6.4点であった。模擬試験における各問の正答率は14.9%～89.4%，平均47.0%，標準偏差19.7%であった。これらの数値は模擬試験中止以前の得点分布と同程度であった。（令和元年度：平均24.2点，標準偏差7.4点，平成30年度：平均26.1点，標準偏差6.4点，平成29年度：平均26.6点，標準偏差5.3点，平成28年度:平均22.4点，標準偏差5.9点）（令和2~4年度は中止のためデータなし）。

以下には今年度の試験問題のうち，正答率40%以下であった問題の解説を示す。



問題 1. HLA の発見について，もっとも適切な記述を a～e のうちから一つ選べ。

a. 腎臓移植を受けた患者血清と他人の白血球の凝集反応により HLA が発見された。

b. 最初に命名された HLA 抗原は HLA-A24 である。

c. 皮膚移植の適合，不適合の解析によって HLA が発見された。

d. HLA を発見したのは Jean Dausset 博士である。

e. 細胞学的 HLA 検査方法を確立したのは Paul Ichiro Terasaki 博士である。

正解：d

正答率 29.8%（代表的な誤答：e）

Jean Dausset 博士は輸血歴のある患者血清中に白血球を凝集させる抗体の存在を見出し，1952 年に報告しており，これを以て HLA 研究の始まりとされている。Jean Dausset 博士が「HLA の父」と呼ばれる所以である。代表的な誤答である e の Paul Ichiro Terasaki 博士の偉業は，血清学的検査法であるリンパ球細胞傷害試験（Lymphocyte cytotoxicity test: LCT）（最近では補体依存性細胞傷害検査（complement dependent cytotoxicity: CDC）ともいわれる）を発明したことであり，本法は通称「テラサキ法」とも呼ばれている。なお，本問は**問題 50** とも関連しているので，そちらの解説も参照されたい。

問題 4. 転写に関して，もっとも適切な記述を a～e のうちから一つ選べ。

a. RNA を構成する糖をデオキシリボースという。

b. 転写はリボソームで行われる。

c. RNA ポリメラーゼは合成のきっかけとなるプライマーを必要とする。

d. 転写において，RNA ポリメラーゼはアンチセンス鎖を 3′ から 5′ 方向に移動する。

e. mRNA の 5′ 末端にポリアデニル酸（ポリ A）鎖が付加される。

正解：d

正答率 29.8%（代表的な誤答：b）

転写の際，RNA ポリメラーゼは二本鎖 DNA のうちの鋳型となるアンチセンス鎖に存在する特定のプロモータ配列に結合し，DNA 配列上を 3′ から 5′ 方向に移動しながら RNA 合成を行う。リボゾームは遺伝子の転写ではなく翻訳に関与するので選択肢 b は誤りである。なお，RNA を構成する糖はリボースであり，ポリアデニル酸（ポリ A）鎖が付加されるのは mRNA の 3′ 末端である。

問題 5. HLA 領域上の次の遺伝子のうち，古典的 HLA クラス I 分子による抗原提示と直接関係しない遺伝子を a～e のうちから一つ選べ。

a. *TAP1*

b. *TNXB*

c. *PSMB9*

d. *TAP2*

e. *TAPBP*

正解：b

正答率 21.3%（代表的な誤答：c）

TNXB は HLA クラス III 遺伝子領域にマップされる遺伝子で，テナシンファミリーメンバーの一つである

Tenascin XB をコードしているが，この分子は細胞外マトリックス糖タンパクであり HLA 分子の抗原提示には関与していない。一方，代表的な誤答である c の *PSMB9* は，以前は *LMP2* と呼ばれていたプロテアソーム関連遺伝子で，20S サブユニットタンパクをコードしている。本遺伝子は HLA クラス II 遺伝子領域にマップされるが，分子は細胞内プロテアソームにおける内因性タンパクのプロセッシングを担い，TAP 分子と共に HLA クラス I 分子による抗原提示に関わっている。

問題 10. HLA-G の機能に関して，誤っている記述を a ～ e のうちから一つ選べ。

a. ホモダイマーを形成する。
b. 自己ペプチドを提示する。
c. β2 マイクログロブリンと会合している。
d. 可溶性 HLA-G 分子は，TCR を介して CD8 陽性 T 細胞を抑制する。
e. 膜結合性 HLA-G 分子は LILR-B2 を介して NK 細胞を抑制する。

正解：d

正答率 23.4%（代表的な誤答：c）

非古典的 HLA クラス I 分子である HLA-G には，膜結合型以外に可溶型が存在する。可溶型 HLA-G 分子は，妊娠初期～中期の胎盤に発現し，CD8 陽性 T 細胞のアポトーシスや CD4 陽性 T 細胞の増殖抑制を誘導することで，母児免疫寛容維持の役割を担っている。これらの反応が TCR を介したものであるという報告は現時点では見られない。代表的な誤答（正しい記述）は c であるが，HLA-G 分子は，古典的クラス I 分子と同様に，クラス I 遺伝子由来の α 鎖と β2 ミクログロブリン（問題文では発音上の問題でマイクログロブリンと記載しているが，日本ではミクログロブリンの表記が一般的である）が会合しており，ペプチド収容溝に内在性ペプチドを結合できる。

問題 11. 非古典的 HLA クラス II 分子（HLA-DO, HLA-DM）に関してもっとも適切な記述を a ～ e のうちから一つ選べ。

a. HLA-DO 分子をコードする α 鎖遺伝子と β 鎖遺伝子は，古典的クラス II 遺伝子と同様に，隣り合って存在している。
b. HLA-DM 分子は HLA-DR 分子への抗原ペプチド結合を阻害する。
c. HLA-DO 分子は，通常は抗原ペプチドを結合できない。
d. HLA-DM 分子と HLA-DO 分子が結合することはない。
e. HLA-DM 分子や HLA-DO 分子の発現異常は自己ペプチドへのトレランス誘導に影響する。

正解：c

正答率 25.5%（代表的な誤答：e）

HLA-DM や -DO 分子は細胞内のリソゾームやエンドソームに局在し，HLA- クラス II による抗原提示に関与しているシャペロン様分子である。HLA-DO 分子のペプチド収容溝は古典的 HLA クラス II に比べると狭く，抗原ペプチドを結合できない（挟めない）ことが報告されている。なお，細胞株やマウスを用いた実験において，DM 分子の発現欠損や DO 分子の強発現が，末梢における MHC クラス II 分子による非自己抗原ペプチドの提示を阻害することが報告されており，これによって免疫不全や自己免疫現象を誘導することが示めされているが，ヒト体内で同様の現象が生じているか否かについては，直接的な証拠の報告はまだない。

問題 12. HLA クラス I 遺伝子の発現制御機構に関して，誤っている記述を a ～ e のうちから一つ選べ。

a. 血小板では，HLA クラス I 分子が発現するが，HLA クラス I 遺伝子の転写はない。
b. HLA クラス I 遺伝子の転写制御領域には，HLA クラス II 遺伝子と同様に，NF-Y が結合する。
c. 異なるローカスの HLA クラス I 遺伝子は転写産物量が異なる。
d. HLA クラス I 遺伝子の転写制御因子 CITA（class I trans activator）は DNA に結合する。
e. HLA クラス I 遺伝子の転写は，TNF や IFN によって誘導される転写因子によって制御される。

正解：d

正答率 23.4%（代表的な誤答：a）

HLA クラス I 遺伝子の転写制御因子 CITA（class I trans activator）は，X1 ボックスの調節因子 X（RFX）複合体（RFX5, RFXANK, RFXAP），X2 ボックスの cAMP-responsive-element-binding protein 1（CREB1）と activating transcription factor 1（ATF1）分子に結合するが，DNA には直接結合しない。また，血小板表

面上にはHLAクラスⅠ分子が発現するが，核は存在しないのでクラスⅠ遺伝子の転写は行われない。NF-Yは種々の遺伝子のプロモーター領域にあるY-boxに結合する転写因子であるが，クラスⅠ遺伝子およびクラスⅡ遺伝子のどちらにもY-boxが存在する。

問題14. 古典的HLA分子による抗原提示に関して誤っている記述の組合せをa～eのうちから一つ選べ。

1. 細胞質内のウイルスやある種の細菌などの非自己タンパク質に由来するペプチドは，主にエンドソームに運ばれてHLAクラスⅡ分子により細胞表面に提示される。
2. 樹状細胞は非自己タンパク質を取り込んで，これに由来するペプチドを，クラスⅠ，クラスⅡのいずれのHLA分子にも提示することができる。
3. 細胞外のタンパク質を取り込み，これがプロセスされて生じたペプチドをHLAクラスⅠに結合して，細胞傷害性T細胞に提示することを交差抗原提示という。
4. 自己のタンパク質よりプロセスされて生じるペプチドは，HLAクラスⅠ，クラスⅡのいずれにも結合しない。
5. 細胞質内のタンパク質の一部は，プロテアソームで分解され，生じたペプチドはTAPにより小胞体内に輸送される。

a 1, 2　b 1, 4　c 2, 3　d 3, 4　e 4, 5

正解：b

正答率　17.0%　（代表的な誤答：d）

外来抗原（寄生虫や細菌などの微生物由来のタンパク質やスギ花粉などの環境中のタンパク質）は細胞内に取り込まれてリソゾームでペプチドへと分解され（外来性ペプチド），エンドソームに運ばれてHLAクラスⅡ分子により細胞表面に提示される。一方，細胞内に存在する自己のタンパク質や，細胞質内で増殖するウイルスや細胞内寄生するある種の細菌由来のタンパク質はプロテアソームで分解され(内在性ペプチド)，TAPトランスポーター分子により粗面小胞体に運ばれてHLAクラスⅠ分子と結合して細胞表面に提示される。従って，選択肢1と4は誤り。その他の選択肢は正しい。

問題17. Th1細胞が直接関与する機能について正しい記述をa～eから一つ選べ。

a. 抗体の産生
b. B細胞の分化促進
c. マクロファージの活性化
d. ウイルス感染細胞の破壊
e. 胸腺における免疫寛容の誘導

正解：c

正答率　23.4%　（代表的な誤答：a）

Th1細胞は，マクロファージや細胞傷害性T細胞等を活性化することにより，これらの細胞が外部より体内に侵入した病原体の排除を促進する。代表的な誤答であるa（抗体の産生）に直接関与しているのはB細胞であり，産生誘導に関わるのはTh2細胞である。

問題19. B細胞レセプター遺伝子（免疫グロブリン遺伝子）に関して誤っている記述をa～eのうちから一つ選べ。

a. 重鎖の可変領域はV，D，Jの3領域の遺伝子再編成によって構成される。
b. 重鎖の可変領域には高頻度に体細胞変異が導入される。
c. 重鎖の定常領域のクラススイッチによってIgM, IgD, IgG, IgE, IgAが生成される。
d. 重鎖の体細胞変異とクラススイッチには同じ酵素が関与している。
e. B細胞レセプターよりT細胞レセプターの方が高度な多様性を獲得している。

正解：e

正答率　21.3%　（代表的な誤答：d）

B細胞レセプター重鎖遺伝子（免疫グロブリンH鎖遺伝子）は，可変領域におけるV，D，Jの3遺伝子による再編成で構成されることに加え，選択肢b, cの様な特徴も併せ持つため，無限に近い多様性を獲得できる。T細胞レセプターのように抗原の認識にMHC分子を必要としないことから，B細胞レセプターの方がより高度な多様性を獲得しているといえる。代表的な誤答の選択肢dにおける重鎖の体細胞変異とクラススイッチの誘導には，activation-induced cytidine deaminase：AIDと呼ばれる酵素が必須である。AIDは本庶佑博士により同定された。なお，cではIgMおよびIgDに関しては，MおよびDからG, A, Eへのクラススイッチが起こる。

問題 21. COVID-19 に関連する記述として誤っている記述を a ～ e のうちから一つ選べ。

a. SARS-CoV-2 感染症であり，2019 年 12 月に中国（武漢市）で初めて確認された。
b. SARS-CoV-2 は細胞内に侵入して ACE2 と結合した複合体を形成する。
c. SARS-CoV-2 の変異速度はインフルエンザウイルスとほぼ同程度である。
d. スパイク（S）蛋白に対する免疫応答を誘導する種々のワクチンが開発されている。
e. 感染者数が減少した 2023 年 5 月に感染症法上の位置づけが 5 類になった。

正解：b

正答率 14.9%（代表的な誤答：c）

SARS-CoV-2 は細胞表面に存在する ACE 2 レセプターと結合して複合体を形成するので，選択肢 b の記述は誤り（正解）となる。c については，SARS-CoV-2 や Influenza A ウイルスはエイズウイルスと同様に RNA ウイルスであり，その変異速度はいずれも動物や DNA ウイルスの変異速度の約 100 万倍と言われている。ここでいう変異速度とは進化における変異定着の速度であるが，ウイルスゲノム配列の解析では SARS-CoV-2 の変異頻度は Influenza ウイルスの 1/2 程度とされている。なお，2023 年 8 月に，培養細胞（Calu-3）に感染させた SARS-CoV-2（武漢株）ウイルスの S 遺伝子と Influenza A ウイルスの NA 遺伝子の配列解析から，SARS-CoV-2 は継代培養あたりの変異出現頻度が Influenza A の約 1/24 であったとの報告もある。ただし，これは培養中に出現する変異を変異有するウイルスにおける総変異数の比較が出現する頻度であり，進化における変異速度とは異なる概念である。

問題 26. 固形臓器移植の予後において HLA マッチの関与が最も少ない臓器を a ～ e のうちから一つ選べ。

a. 腎臓
b. 心臓
c. 肝臓
d. 肺
e. 小腸

正解：b

正答率 25.5%（代表的な誤答：c）

固形臓器移植においては，心臓移植と HLA マッチ度は予後に関連しないとの結果が報告され，コンセンサスとなっている。一方，肝臓移植については弱いながらも関連が報告されている。なお，肝臓移植においては，ドナーが HLA ホモ接合である場合，当該 HLA を有するレシピエントへの移植は禁忌である。

問題 30. HLA と自己免疫疾患が関連するメカニズムとして，もっとも考え難い仮説を a ～ e のうちから一つ選べ。

a. 疾患関連 HLA が T 細胞に自己抗原を提示する。
b. 疾患関連 HLA が B 細胞に自己抗原を提示する。
c. 胸腺において疾患関連 HLA が自己反応性 T 細胞を増幅する。
d. 末梢リンパ節において自己抗原に反応する B 細胞が増殖する。
e. 疾患関連アレルと連鎖不平衡にある病因遺伝子アレルが疾患発症に関与する。

正解：c

正答率 29.8%（代表的な誤答：d）

自己反応性 T 細胞は，胸腺における分化の過程で，胸腺髄質におけるいわゆる「負の選択」によって通常は細胞死により排除されるが，これを逃れて末梢に未成熟な T 細胞の状態で出現することがあり，これが何らかのメカニズムにより活性化されることが自己免疫疾患を発症するきっかけとなる。よって，胸腺内において疾患関連 HLA が自己反応性 T 細胞を直接増幅させることは考え難い。代表的な誤答である選択肢 d については，自己抗原が B 細胞レセプターと結合した際に，T 細胞から放出されたサイトカイン等の刺激によって B 細胞が増殖，分化すると，自己抗体が産生される。

問題 31. HLA に連鎖した免疫不全症の原因として，誤っているものを a ～ e のうちから一つ選べ。

a. *TAP1* 欠損
b. *TAP2* 欠損
c. *LMP2* 欠損
d. *LMP7* 欠損
e. *B2M* 欠損

正解：e

正答率 29.8%（代表的な誤答：d）

β2-ミクログロブリン（B2M）をコードする *B2M* 遺伝

子は第15染色体に位置するため，第6染色体に位置するHLAや，HLA遺伝子領域に存在する他の選択肢とは連鎖不平衡の関係にはない。B2M欠損症では，*B2M*遺伝子異常による分子発現の低下や欠損が生じ，HLAクラスI分子とB2Mとの正常な複合体形成が行えず，細胞表面への発現が見られなくなる。その結果，CD8陽性細胞の活性化が抑制されるという機能的要因により免疫不全症が発生する。

問題34. 遺伝学的診断法に関して誤っている記述をa～eのうちから一つ選べ。

a. 非侵襲的出生前検査（NIPT）によるダウン症候群の陽性的中率は約97%である。
b. 非侵襲的出生前検査（NIPT）は染色体異常症のスクリーニング検査として開発された。
c. がん細胞特異的体細胞遺伝子変異の検出は血液を用いて実施できる。
d. 大腸がんや乳がんの5-10%は常染色体性劣性遺伝形式をとる遺伝病である。
e. DTC（Direct to Consumer）検査とは医療者が関わらない遺伝子検査である。

正解：d

正答率　36.2%　（代表的な誤答：e）

大腸がんや乳がんの5-10%を占める遺伝性大腸がん（リンチ症候群や家族性大腸ポリポーシス（familial adenomatous polyposis:FAP）など）や遺伝性乳がんは，常染色体優性（顕性）遺伝形式をとる。他の選択肢は正しい。

問題38. Primed lymphocyte test(PLT)について，誤っている記述をa～eのうちから一つ選べ。

a. PLT検査により検出できるのはHLA-DP抗原の相違である。
b. PLT検査は刺激細胞，反応細胞ともにリンパ球を使用する。
c. PLT検査は，MLRにより増殖した被験者由来B細胞の反応で識別される。
d. HLA-DP抗原特異性を検出するアロ抗血清は存在しない。
e. PLT検査は手技が煩雑であるため，現在ではDNAタイピングが主流である。

正解：c.

正答率　14.9%　（代表的な誤答：d）

PLT検査は，細胞学的なHLA多型の検査法の一つとして，HLA-DP抗原のタイピングに用いられている検査法である。本法はHLA-D特異性が一致しHLA-DP特異性が異なるアロリンパ球の，混合リンパ球培養反応（mix lymphocyte reaction: MLR）により生じたアロHLA-DP感作T細胞に，増殖抑制処理した被験者細胞を加えて二次刺激を与えるにより発生するT細胞応答を観察することにより，HLA-DP抗原の多型を検出できる。HLA-DP抗原を認識する特異的アロ抗血清が存在しなかったことから，以前は本法がDPタイピングに用いられていたが，手技が煩雑であるため現在ではDNAタイピングが主流である。

問題41. HLA抗原とアレルの表記について，正しい記述をa～eのうちから一つ選べ。

a. HLA-B*75及びHLA-B*76は，HLA-B15抗原群のアレルである。
b. HLA-B40グループの抗原は，HLA-B*60およびB*61アレルで表記される。
c. HLA-Bw4抗原のアレルはHLA-B*04で表記される。
d. HLA-B75, 76, 77抗原は，HLA-B*15アレルで表記される。
e. HLA-A*09アレルは，HLA-A9抗原群のアレルである。

正解：d

正答率　36.2%　（代表的な誤答：b）

令和4年度問題33の類似問題である。HLA-B75, -76, -77抗原は，HLA-B15抗原より派生したスプリット抗原であるが，WHO命名委員会の例外的ルールが適用され，アレル表記は元の抗原名であるHLA-B*15となる。したがって，選択肢aに示すようなアレルは存在しない。同様の理由から，代表的な誤答である選択肢bの場合，HLA-B40抗原グループのスプリット抗原に対応するアレルはHLA-B*40で表記される。詳細は　2023年度認定HLA技術者講習会テキスト（http://jshi.umin.ac.jp/jounals/file/MHC3002_01_kosyukaiN.pdf）の表1を参照されたい。

問題42. 下の表は日本人集団に多く観察されるHLA-A-B-DRB1ハプロタイプである。高頻度の1～5位のハプロタイプのうち，誤っているものをa～eのうち

日本人集団に多く観察される HLA-A-B-DRB1 ハプロタイプと頻度

順位	ハプロタイプ			ハプロタイプ頻度（%）	陽性者頻度（%）
1	A*24:02	B*52:01	DRB1*15:02	8.5	16.2
2	A*33:03	B*44:03	DRB1*13:02	4.7	9.3
3	A*24:02	B*07:02	DRB1*01:01	3.7	7.3
4	A*11:01	B*54:01	DRB1*04:05	2.6	5.1
5	A*02:07	B*46:01	DRB1*08:03	1.8	3.5

から一つ選べ。

a. 1 位

b. 2 位

c. 3 位

d. 4 位

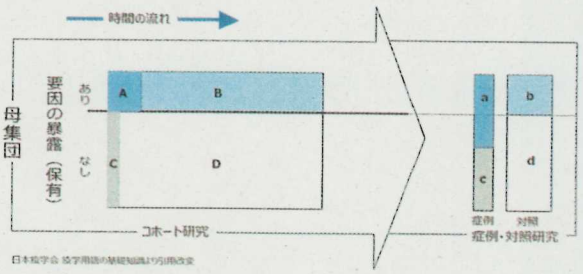
e. 5 位

正解：d

正答率 23.4% （代表的な誤答：c）

日本人集団に多く観察される HLA ハプロタイプとして 4 位に示されている頻度は，正しくは *A*24:02-B*54:01-DRB1*04:05* ハプロタイプのものである。*HLA-B*54:01* と *-DRB1*04:05* アレルは強い連鎖不平衡の関係にあるが，HLA-A-B-DRB1 の 3 遺伝子座間のハプロタイプ構成をみると *HLA-A*24:02* の他に *-A*11:01* においても連鎖不平衡が存在する。ちなみに *A*11:01-B*54:01-DRB1*04:05* ハプロタイプの頻度は 0.8~0.9% で 9 位である。この様な統計データは数か所から公式に報告されているが，頻度，順位とも概ね同様である。

問題 48. 次の図はコホート研究と症例・対照研究の概念を示している。この図の説明として，誤っている記述の組合せを a ～ e のうちから一つ選べ。



1. この図は，罹患率が高い疾患についてのコホート研究と症例・対照研究の概念図である。
2. コホート研究では，要因の有無で区分した集団について，時間を追って発症の有無を検討する。
3. 症例・対照研究では，ある時点での罹患者と非罹患者について，要因の有無を検討する。
4. コホート研究の罹患 / 非罹患オッズ比は AD/BC で求められる。
5. 症例・対照研究の罹患 / 非罹患オッズ比は ac/bd で求められる。

a 1, 2　b 2, 3　c 3, 4　d 4, 5　e 1, 5

正解：e

正答率 25.5% （代表的な誤答：d）

コホート研究とは，要因の暴露の有無で区分した集団について，時間を追って発症の有無を追跡し，要因と疾患の関係を検討する前向き研究である。図の左側に示されたコホート研究の概念では，A および C が発症している割合を指すので，選択肢 1. にある罹患率が高い疾患とはいえない。また，選択肢 5. の症例・対照研究の罹患 / 非罹患オッズ比は，患者（症例）での a/c を対象での b/d で除したものとなるため，ad/bc で求められる。

問題 50. HLA に関連する以下の出来事のうち，誤っているものを a ～ e のうちから一つ選べ。

a. リンパ球細胞傷害性試験（LCT）法の発明

b. 第 6 回国際 HLA ワークショップでの HLA-D 特異性同定

c. マウス H2 領域の発見

d. G. D. Snell, D.B. Amos らがノーベル医学生理学賞を

受賞

e. PCR を用いた DNA タイピング法の普及

正解：d

正答率 25.5%（代表的な誤答：b）

本問は，ここ数年出題した過去問題を改変したものである。マウス H2 領域の発見に関わった G. D. Snell，B. Benacerraf，そして HLA の父と呼ばれる J Dausset の 3 氏は，「免疫反応を調節する細胞表面の遺伝的構造に関する研究」の功績により，1980 年にノーベル医学・生理学賞を受賞したが，この中に D.B. Amos 博士は含まれていない。D.B. Amos 氏は，1964 年に世界で初めて開かれた国際組織適合性ワークショップを主催し，本ワークショップで 3 つの特異性が同定された。本問に関する内容については，以下に示す 2021 年度認定 HLA 技術者講習会テキストの表 2 を参照されたい。

https://www.jstage.jst.go.jp/article/mhc/28/2/28_77/_pdf/-char/ja

SSY［腎 3］-5　Nephron mass定量化による生体腎移植後グラフト機能予測

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西山　博之[1]、小田　竜也[3]、湯沢　賢治[1]、山縣　邦弘[4]

【背景】生体腎移植後早期腎機能は、グラフトの「nephron mass」に依存する。近年、CT撮影装置の発展とCT-volumetryの改良により、正確的に「nephron mass」を測定できるようになった。本研究では、CT-volumetryを用いてグラフト「nephron mass」を定量化し、これを用いたcortex/recipient weight ratio(CRWR)が、他パラメータと比較し、術後早期腎機能予測が可能か検証した。【方法】2014年1月～2022年12月までに生体腎移植を受けた107人を対象とし、開発コホート（n=79）と検証コホート（n=28）に分けた。開発コホートを用い、CRWRを含むパラメーターと術後eGFRとの相関係数を算出した。重回帰分析より、術後1ヶ月eGFR予測式を作成した。検証コホートを用いて、その妥当性を検討した。【結果】相関係数はCRWRが最も高かった（1ヶ月r=0.66）。CRWRは術後1と6ヶ月で、尿蛋白と弱い逆相関を示した（r=-0.27とr=-0.34）。重回帰分析により、1ヶ月後のeGFRは線形モデルで予測された：0.23 x ドナー術前eGFR + 17.03 x CRWR + 8.96 x 先行的腎移植 + 5.10. 検証コホートの大部分の患者において、観察されたeGFRは予測されたeGFRから±10 ml/min/1.73 m^2の範囲内にあった。【結論】CRWRは、初期の移植片機能を予測するための正確なパラメータであった。この式を用いた腎機能の予測は、適切なドナーを選択し、不必要な術後医療介入を回避するために有用であると考えられる。

Kienböck病の病態について

The condition of Kienböck disease

小川 健[1]

Summary いまだに答えの出ないKienböck病の病態ではあるが，そのため多くの研究がなされ，少しずつ着実に前進している。本稿では，その疫学，成因，解剖学的特徴，MRI，年齢による違いについて解説するとともに，自験例を踏まえて考察を加え，いまだに明確になっていないその病態を考察する。

Key words キーンベック病（Kienböck disease），うっ血（blood congestion），Lichtman分類（Lichtman classification），造影MRI（enhanced MRI）

はじめに

月状骨が外傷後もしくは特発的に壊死する月状骨軟化症は，1910年にオーストリアの放射線科医であるRobert Kienböck[1]により最初に報告され，現在では広くKienböck病とよばれている。月状骨の解剖学的特性は，手根骨の中央に位置し，周囲の大部分を軟骨と皮質骨に囲まれた骨で，血管の流入は手関節掌側と背側の靱帯付着部に限られるということである[2]。そのため，一度壊死に陥った月状骨組織は自発的再生が得られにくく，圧潰が起こり，手根骨全体の並びが崩れるため，手関節機能に大きく影響を与える。その原因や病態については，解剖学的な血流障害や骨折の遷延治癒状態[1]，反復微小外力に伴う月状骨内圧の上昇[3]，橈尺骨長不均衡による月状骨への応力集中[4]など，諸説が提唱されているが，症例による違いもあり，複合的な要因と考えるべきである。

本稿では，近年の研究報告を中心に解説し，いまだ未解明な部分も残されているKienböck病の病態を少しでも解きほぐせたらと考えている。

頻度

2016年の大規模(50,171人)調査において，Kienböck病の頻度は0.27%（138人），その内訳は無症状が0.1%，有症状は0.17%と報告された[5]。アメリカのデータであるが過去最大規模の調査であり，年齢も広範囲にわたっており信頼性は高いといえる。わが国では，清重ら[6]が山形県の65歳以上の検診で520名の単純X線検査にて，その頻度は全体で2.5%，男性4.5%，女性1.3%と報告した。Tsujimotoら[7]は65歳以上の女性を調査し，1.2%と報告した。また，2009年の南アフリカからの報告では，1,287人中23人(1.9%)にKienböck病を認め，その男女比はおよそ6：4で，平均年齢は男性49歳，女性46.5歳であった[8]。一般的に20～40歳の青壮年期の男性で重労働者，マニュアルワーカーに多いといわれているが，年齢による発症病態に違いがある可能性もあり，ある程度の目安と考えるべきであろう。

発症の要因

Kienböck病の原因や病態については諸説あるが，いまだ未解明な部分も残され結論に至らない。

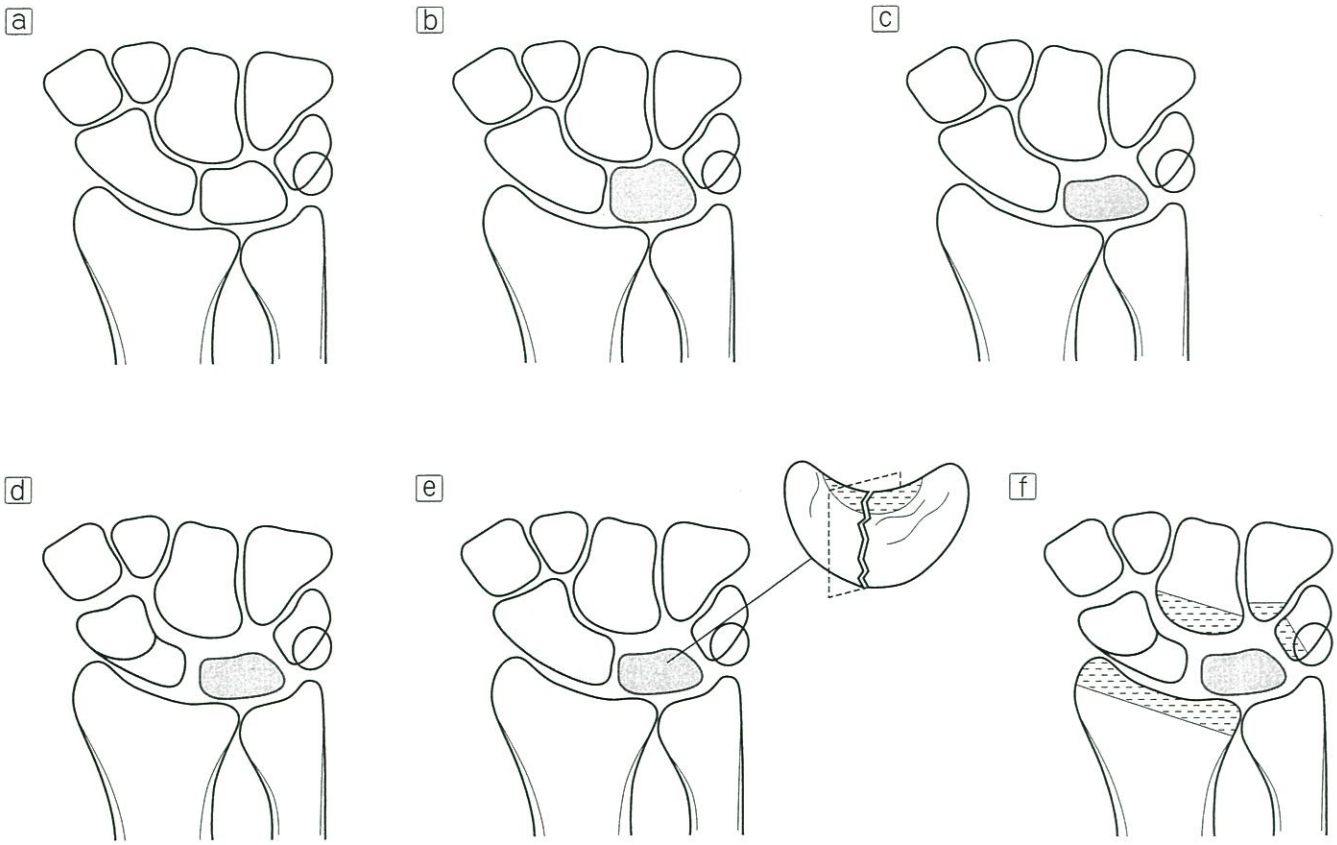
1. Ogawa Takeshi：独立行政法人国立病院機構水戸医療センター整形外科

その発症には，静脈が関与し，まず静脈の閉塞から始まるという考えが，病期の進行過程を考えたうえで，非常にわかりやすい。静脈閉塞によるうっ血で濃縮されたカルシウムを使って骨梁に添加骨を形成しつつ壊死が起こり，壊死に陥った骨梁は徐々に吸収され，骨の強度は次第に低下し軟化をきたす。さらに手関節を使い続けると，月状骨周囲の軟骨は次第に摩耗し，関節症が発生するといった自然経過を上羽[9]が記述している。1996年にSchiltenwolfら[3]も静脈うっ血が発症原因ということを提唱したが，その後の進展はみられなかった。2018年にIchinoseら[10]は，Kienböck病でみられる手関節背側の腫脹に着目し，Kienböck病ではまず外傷または月状骨周囲の炎症によって血管の機能不全が引き起こると考えた。これは大腿骨頭壊死症が静脈うっ血に起因することに類似し，月状骨背側掌側の関節包靱帯にある静脈叢の破綻によるうっ血が月状骨壊死の原因ではないかと考察している。このような静脈の閉塞を引き起こす要因が，外傷や繰り返される微小外力とすると一元的に考えることができる。さらにこの病期を単純X線像のLichtman分類と合わせるとさらに理解しやすい[11]**(図1)**。

(1) うっ血期(Lichtman分類stage Ⅰ)

繰り返される手関節運動または強い外傷により手関節炎が起こると，手関節の腫脹や疼痛などの症状が出現する。滑膜炎の悪化により手関節内圧が上昇し，圧迫力に弱い細静脈が閉塞する。特に，橈骨舟状月状骨靱帯の中にある静脈が関与する。

図1 改訂版Lichtman分類



a：stageⅠ…単純X線では正常
b：stageⅡ…骨硬化像がみられる
c：stageⅢA…圧潰が始まる
d：stageⅢB…圧潰が進行し，手根骨配列が乱れる
e：stageⅢC…冠状面での分節化
f：stageⅣ…関節症性変化がみられる

手関節内の静脈が強く圧迫されると月状骨内にうっ血が生じ，月状骨の内圧が上昇する。動脈血は月状骨内に流入できなくなり，酸素供給を断たれた骨細胞は次第に死に至り，骨壊死に陥る。

(2) 壊死期 (Lichtman分類stage II)

月状骨が壊死に陥るが，うっ血で濃縮されたカルシウムを使って骨梁に添加骨形成を起こし，単純X線像では月状骨全体に骨硬化像を呈する。

(3) 軟化期 (Lichtman分類stage III)

月状骨はいったん壊死に陥るが，壊死に陥った骨梁は徐々に吸収され，骨の強度は次第に低下する。ここでさらに外力が加わる，または骨粗鬆化があると容易に骨折が起こり，月状骨は圧潰を起こしstageⅢAとなる。さらに外力が反復されると圧潰は進行しstageⅢBとなる。ときに，冠状面で分節化することがあり，これをstageⅢCとして，2010年にLichtman自身が改訂版を発表した[11]。

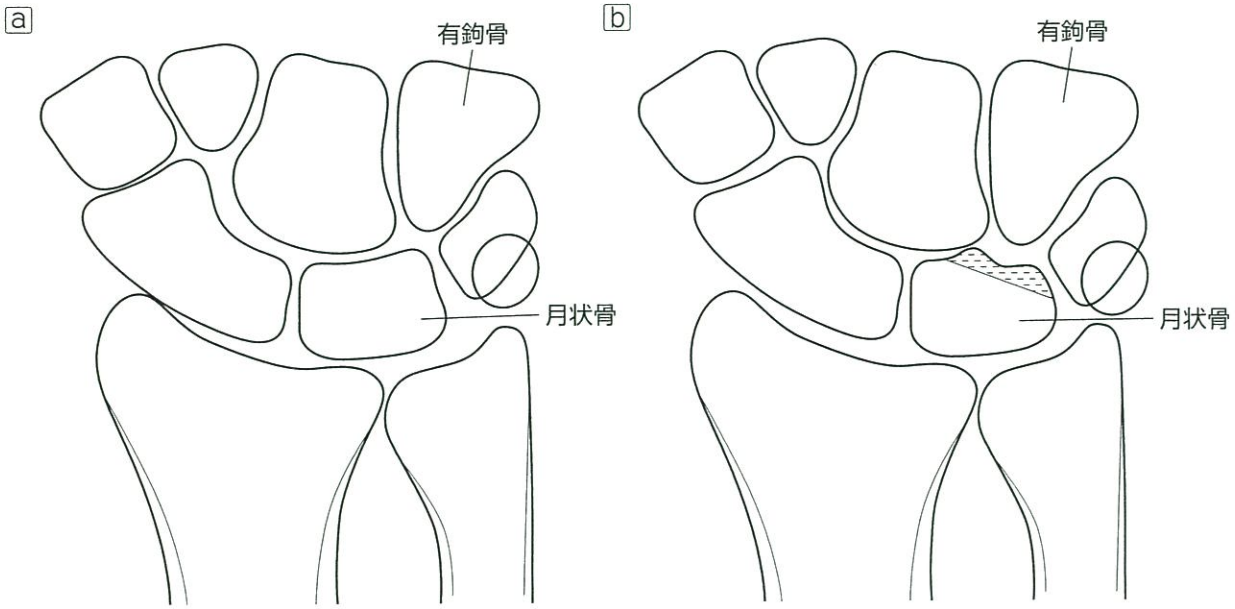
(4) 摩耗期 (Lichtman分類stage IV)

圧潰し変形した月状骨周囲の手根骨軟骨面は，次第に摩耗し関節症を惹起する。高齢者で偶発的に月状骨の変形と関節症が見つかり，疼痛の既往がないという患者もいるが，それは軟化期に大きな外力が加わらずに経過し，この時期になって痛みを自覚するようになったものと推察できる。

X線像における特徴

Kienböck病のrisk factorとしてulnar variance (UV) minusを指摘する報告があるが，いまだ一定の見解は得られていない。1928年にHulten[4]がスウェーデンの疫学調査により，最初に報告して以来，反対意見も含め多数の報告がある。また，月状骨－有鉤骨間に関節形成のあるもの(typeⅡ lunate)も有鉤骨から月状骨への応力が加わりrisk factorとなりうる可能性が示唆されている[12] **(図2)**。中村ら[12]は，剛体ばねモデルによる応力解析において，typeⅡ lunateでは月状骨有鉤骨関節面から月状骨に応力が集中しやすく，関節面の幅が増大するにつれ応力が有意に増大したと述べている。筆者ら[13]は，75例のKienböck病患者の手関節単純X線像をpropensity score matchingで抽出した外傷患者の健側手関節79手と比較し，UV minusはその発症に関与する可能性が高いこ

図2 TypeⅠ lunateとtypeⅡ lunateの違い



a：typeⅠ lunate…有鉤骨との関節面を有さない
b：typeⅡ lunate…有鉤骨との関節面を有する

とを報告した。また，typeⅡ lunate の関与は見出せなかったが，UV minus かつ typeⅡ lunate を有する手関節は，Kienböck病患者で有意に多かった。

年齢による病態の違いはあるか

10歳台と高齢者では，病態が違うのではないかといわれており，14歳以下では軟化期以降の修復過程は成人とはやや異なるとも報告されている[14]。逆に高齢者では骨粗鬆症が関連し，月状骨の圧迫骨折が先行し異なった発生機序をもつことも報告されている[15]。さらに，50歳以上でKienböck病と診断された患者は，保存治療で良好な経過をたどることが多いため，手術介入は熟慮すべきという報告も出てきている[16]。

症例提示

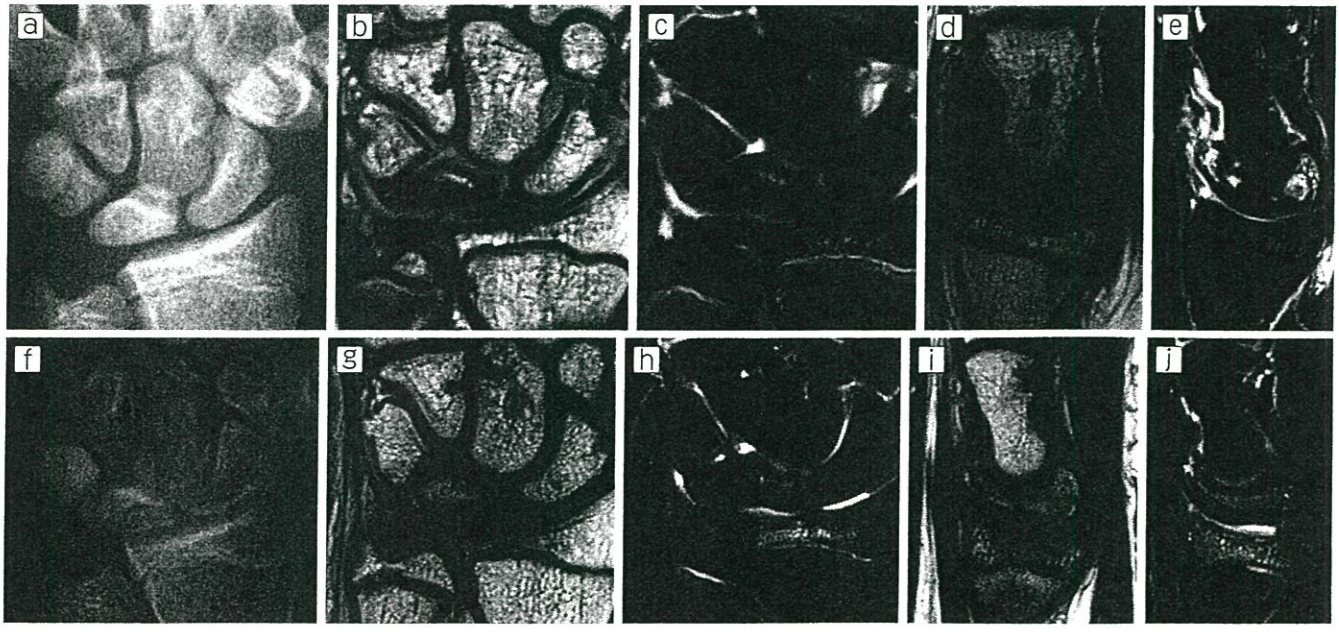
14歳，男児。ボート競技の選手で，左手Kienböck病 Lichtman 分類 stageⅢA。CT 画像でも圧潰が明らかであったが，保存的に治療した。1カ月間の肘下ギプス固定後，さらに2カ月間の肘下シーネ固定で安静を図った。痛みは1カ月で軽減し，6カ月後のX線像でわずかに圧潰が進行していることを認めたが，痛みはなく競技に復帰できた。MRI画像では，軽度圧潰の状態で月状骨の信号が正常化していく変化が認められた**(図3)**。

このように10歳台の症例では，まずは外固定による保存治療を行ってみるべきである。そして，手術治療に際しては，低侵襲な方法を考慮すべきである。

MRIは病状を反映しているのか

Kienböck病の月状骨は壊死骨であり，一般的にはT1強調像，T2強調像ともに低信号を呈する。しかし，特にT2強調像は病期によって，高信号を呈する時期もある。うっ血期や圧潰が起こって間もない時期は，水成分を反映し高信号を呈する。筆者ら[17]が行った先行研究では，組織学的な骨壊死の状態をよく反映しているのはT1強調像で

図3 症例の画像所見



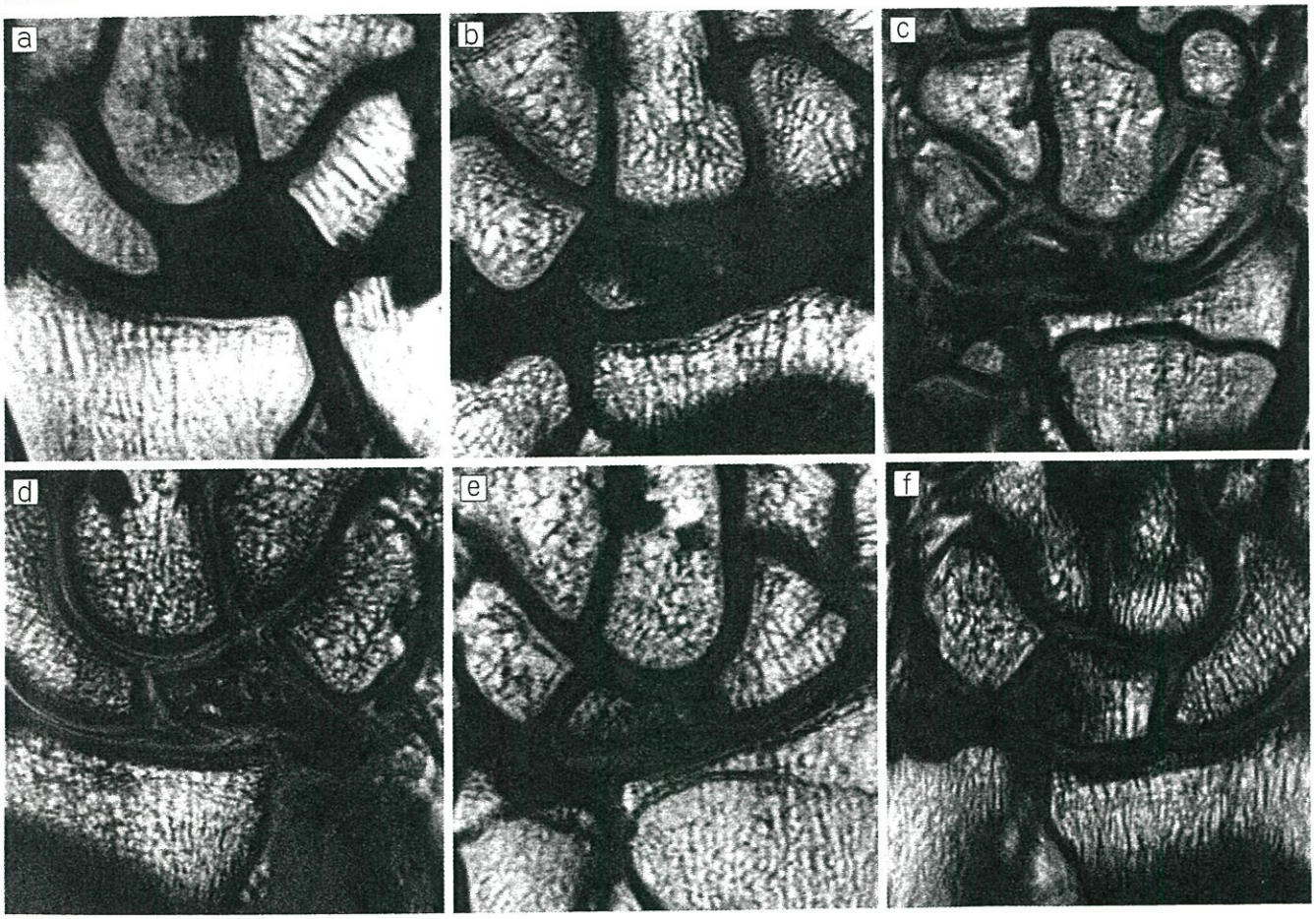
a～e（上段）：初診時
a：単純X線
b：MRI プロトン強調冠状断像
c：MRI 脂肪抑制冠状断像
d：MRI プロトン強調矢状断像
e：MRI 脂肪抑制矢状断像

f～j（下段）：6カ月後
f：単純X線
g：MRI プロトン強調冠状断像
h：MRI 脂肪抑制冠状断像
i：MRI プロトン強調矢状断像
j：MRI 脂肪抑制矢状断像

あった。そして，その程度を評価する指標として，月状骨の信号強度をほぼ正常なgrade 1から完全に低下したgrade 5の5段階に分類したgrading systemを提唱した[18]。**図4**に6症例のMRI T1（プロトン）強調像を示す。Kienböck病では，**図4a**のように月状骨全体が低信号を呈することが多いが，**図4b～e**のように部分的に低信号であったり，低信号の程度が軽度である症例も存在する。一方，尺骨突き上げ症候群でみられるkissing lesionは低信号領域が尺側近位に限局するため，低信号領域が橈側や遠位に及ぶKienböck病とは鑑別が必要である。

Schmittら[19]は，ガドリニウムによる造影MRIの必要性を指摘した。T1低信号だけでは骨壊死の判定はできず，その造影効果がポイントであると述べ，その造影効果の違いにより3つのtypeに分類した。よく造影されるものがtype Aで病理像としては骨髄浮腫の状態，部分的に造影されるものがtype Bで部分的な骨壊死，まったく造影されないものがtype Cで完全な骨壊死である。また，造影MRIからSIR（signal intensity ratio）を算出することで，月状骨内の血流を定量的に評価することができる[20]。高橋ら[21]は，造影から10分間のSIRカーブを描出し，「A：骨髄内血管床増加」，「B：骨髄のうっ血」，「C：虚血」と3つのタイプに分類した。SIRカーブの形状により，月状骨内の血流状態を定量的・視覚的に区別でき，さらに標的範囲を絞ることで月状骨の壊死範囲を特定することも可能であるため，今後の発展が期待される。

図4　MRI T1（プロトン）強調像



a～e：Kienböck病症例
f：尺骨突き上げ症候群症例
Kienböck病では，**a**のように月状骨全体が低信号を呈することが多いが，**b～e**のように部分的な低信号を示すことや低信号の程度が軽度である症例も存在する

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Kienböck病に対する自己骨髄血移植治療

Bone marrow transfusion for Kienböck disease

小川 健[1]

Summary 橈骨または腸骨から吸引採取した骨髄血を月状骨に注入移植し，創外固定と低出力超音波を併用する治療を開始して20年が経った。本稿では，本法を行った51例の成績をまとめ，本法の適応について考察する。また，手術と治療プロトコールを詳しく説明し，tipsを書き添える。

Key words キーンベック病（Kienböck disease），骨髄血移植（bone marrow transfusion），創外固定（external fixation），低出力超音波（low intensity pulsed ultrasound；LIPUS）

はじめに

Kienböck病の治療，特に手術方法は多岐にわたっているが，Lichtman分類でstageⅢAまでは，いずれの治療法も優劣を付けがたいものがある[1]。よって，治療法選択を考えた際に，いかに低侵襲で月状骨の再生を図るか，ということに主眼が置かれる。Kienböck病の低侵襲手術治療として，過去には骨穿孔[2]，創外固定[3]，低出力超音波（low-intensity pulsed ultrasound；LIPUS）[4]などの報告があるが，いずれも効果不十分と結論付けられている。そこで，筆者ら[5]はこれらを組み合わせ，さらに骨髄血移植を追加することで，壊死骨の再生が得られるのではないかという考えのもとに，併用治療法を考案し，その結果を報告した。落合[6),7)]が考案したこの骨再生治療は，橈骨から吸引採取した骨髄血を月状骨に注入移植し，創外固定とLIPUSを併用するといったものである。手技的には簡便であるにもかかわらず，既存の治療法と同等の治療成績であり，MRIにおいても約6割の症例で月状骨の信号回復を認めた。当初は橈骨から採取した骨髄血を移植骨髄血として用いていたが，その後，腸骨からの骨髄血を移植するように変更した[8]。しかし，どちらの骨髄血を用いても術後臨床成績，画像所見ともに有意な差はなく，間葉系幹細胞以外の要因も月状骨の再生に関与していることが示唆された[9),10)]。本法は，最初の発表から20年が経とうとしているが，筑波大学およびその関連施設以外からの報告は見当たらず，国内において幅広く一般化した方法とはいえない。少しでも整形外科医へ周知できるよう，本稿ではKienböck病に対する自己骨髄血移植治療の実際について解説し，その成績を報告する。さらに，本法の裏付けとなる基礎研究についても簡単に報告し，本法の適応を考察する。

対象および方法

2000年5月～2022年1月までに，Kienböck病に対して本法を行い，1年以上経過観察できた51例を対象とした。男性29例，女性22例で，右手25例，左手26例であった。術前Lichtman分類

1. OGAWA Takeshi：独立行政法人国立病院機構水戸医療センター整形外科

は，stageⅡ 12例，ⅢA 25例，ⅢB 14例であり，移植骨髄血は橈骨が24例，腸骨が27例であった。橈骨骨髄血を移植した症例のみをまとめた報告[5)~7)]や腸骨骨髄血移植と比較した報告[9)]が過去に出版されているので，併せて参照いただきたい。本稿では，全例を対象に結果を報告する。評価は，最終診察時のMayo wrist score，単純X線像のcarpal height ratio（CHR），Stahl index（SI），そしてMRI検査である。MRI検査は，筆者ら[11)]が報告したordinal scaleを用いて，月状骨の信号強度をほぼ正常なgrade 1から完全に低下したgrade 5まで5段階に分類し，手術前後で比較した（Ogawa's grade）。統計はt検定を用いて，$p<0.05$を有意とした。

手術と治療プロトコール

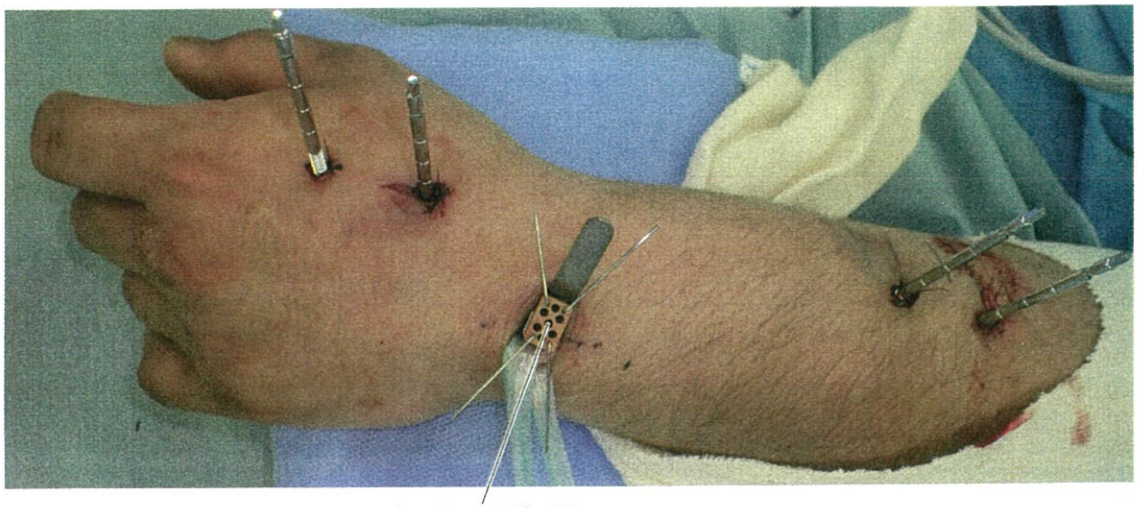
① 全身麻酔にて行い，透視下に創外固定ピンを第2中手骨と橈骨に2本ずつ挿入する。橈骨から骨髄血を採取する際は，ここで吸引採取していたが，腸骨骨髄血を用いる場合はピンを立てるのみである。

② 月状骨に背側よりアプローチすべく，手関節背側中央に3cmの横皮切を置き，伸筋支帯を第4区画で開放し，伸筋腱を避けて関節包を露出する。関節包は切開せず，専用のドリルガイド（月状骨ドリルガイド®，イソメディカルシステムズ社）を設置し，4隅を0.8mm径ワイヤーで固定する（**図1**）。直径2mmのストッパー付き専用ドリルで月状骨背側皮質のみ穿孔する。このドリルガイドはX線透過性となっており，透視下に月状骨直上に設置することが可能で，8カ所穿孔できるように作製されている。透視で確認し，至適位置3カ所を穿孔できれば十分であり，穿孔しすぎると月状骨の背側皮質を壊し逆効果になりかねない。

③ 腸骨から吸引採取した骨髄血（**図2**）を直接，5mL程度月状骨に注入移植する。10mLシリンジを用いて吸引採取し，18G針にて月状骨内の骨梁の間隙に骨髄血を染み渡らせるイメージでゆっくりと注入することがコツである。月状骨の体積からすると2mL程度が限界と考えられ，5mL入れても関節内やガイドホールから漏れ出てしまうが，少なすぎるよりはよいため許容している（**図3，4**）。各種サイトカインや液性因子など，間葉系幹細胞以外の成分も壊死骨の再生には関与していると考えているため[9),10)]，あえて遠心分離にて濃縮することは行わず，吸引採取した血液が凝固する前にすばやく移植している。

④ 伸筋支帯を縫合して閉創し，創外固定をセットする。創外固定は，手関節を掌背屈中間位で軽度牽引した状態で固定する（**図5**）。機種は，当初からステーブルロック®（小林メディ

図1　創外固定ピンと専用ドリルガイドを設置



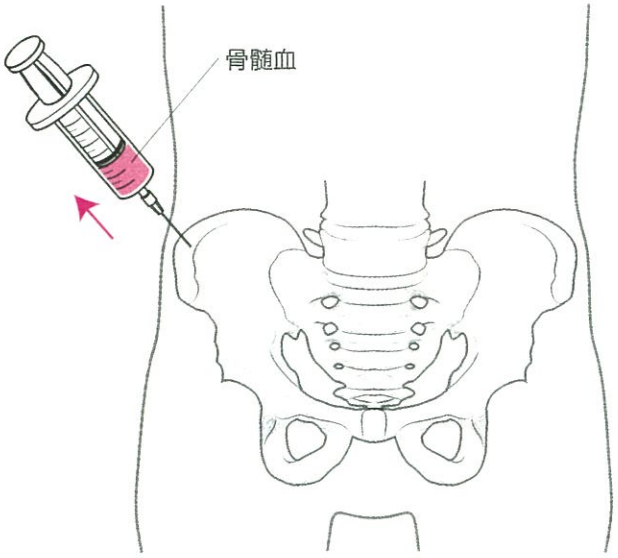
カル社）を用いてきたが，何を使ってもよいと考えている。

⑤術後，可及的早期からLIPUSを開始し，3カ月間行う（**図6**）。LIPUS期間は，当初は4カ月以上1年を目安に行っていたが，患者コンプライアンスの問題や保険請求も加味し，現在は3カ月間としている。

⑥創外固定は，術後8週で抜去し，可及的に可動域訓練を進める。創外固定期間は，一時期3カ月としたこともあったが，2カ月間と比較して臨床成績に差がなかったことから，現在は2カ月としている[9]。経過中にピン感染を認め，シャワー洗浄などでも感染が持続するようであれば，時期が早くとも迷わず抜去する。その場合は，術後8週までシーネ固定を行う。

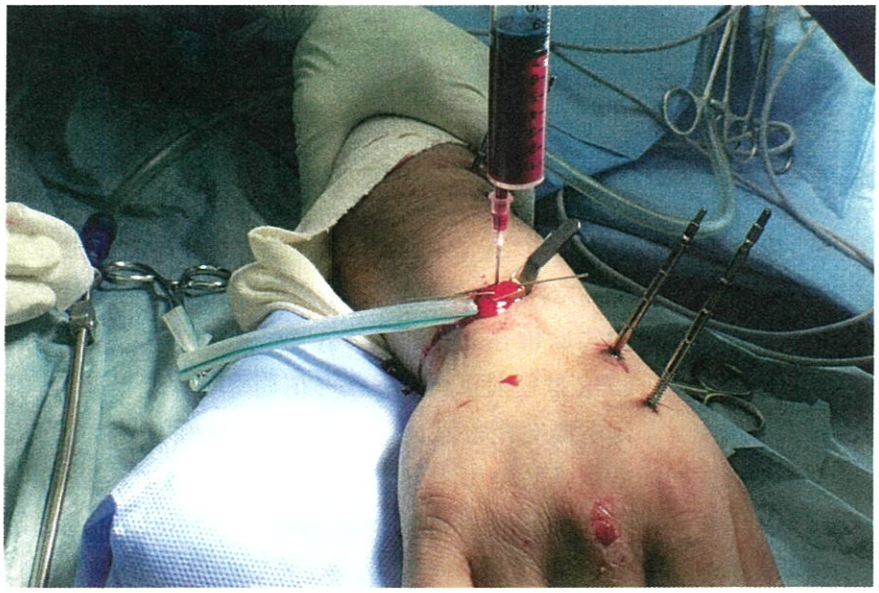
⑦術後3カ月でLIPUSを終えた頃から，痛みに応じて仕事のレベルを上げていく。

図2　骨髄血採取



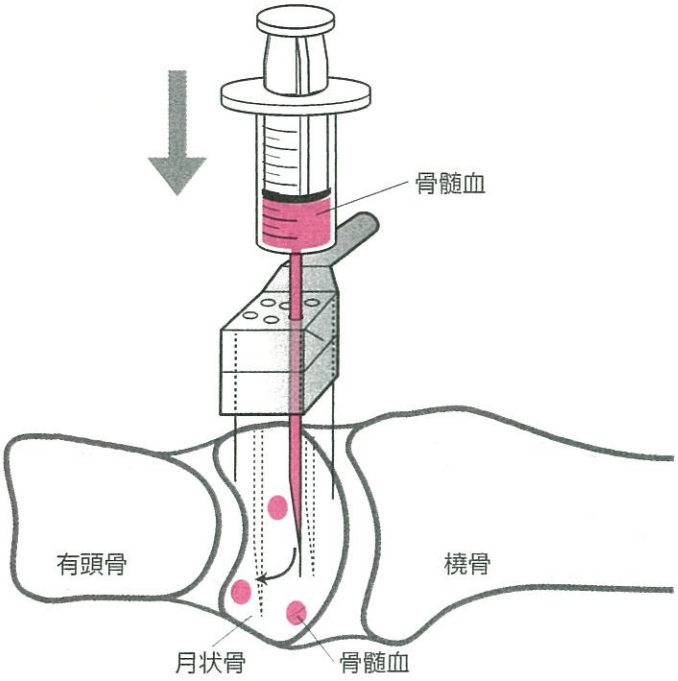
骨髄穿刺または18G針を用いて，10mLシリンジで吸引採取する

図3　骨髄血移植①



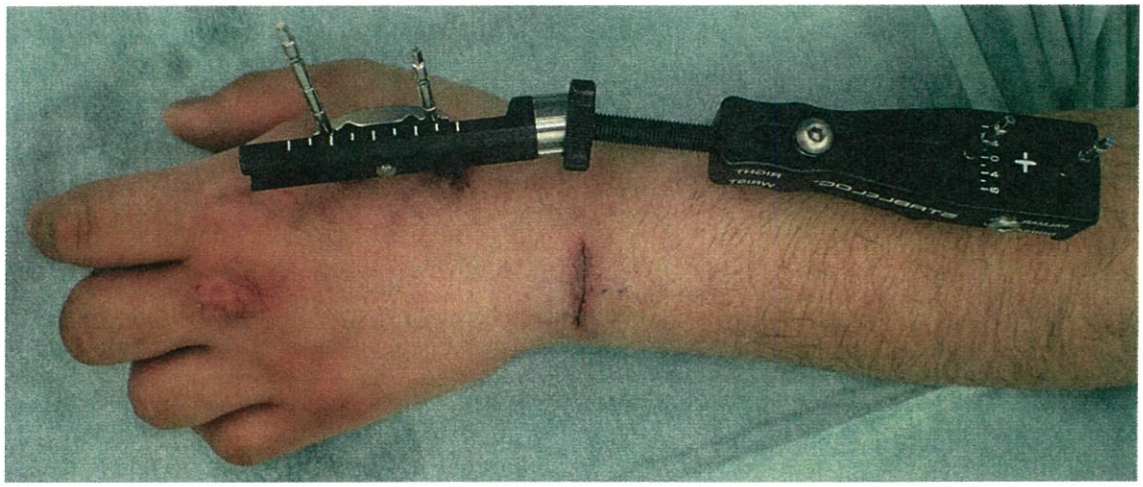
5mLでも関節内やガイドホールから漏れ出てくるが，多めに入れる

図4 骨髄血移植②



月状骨内の骨梁の間隙に骨髄血を染み渡らせるようゆっくりと数カ所から注入する

図5 創外固定

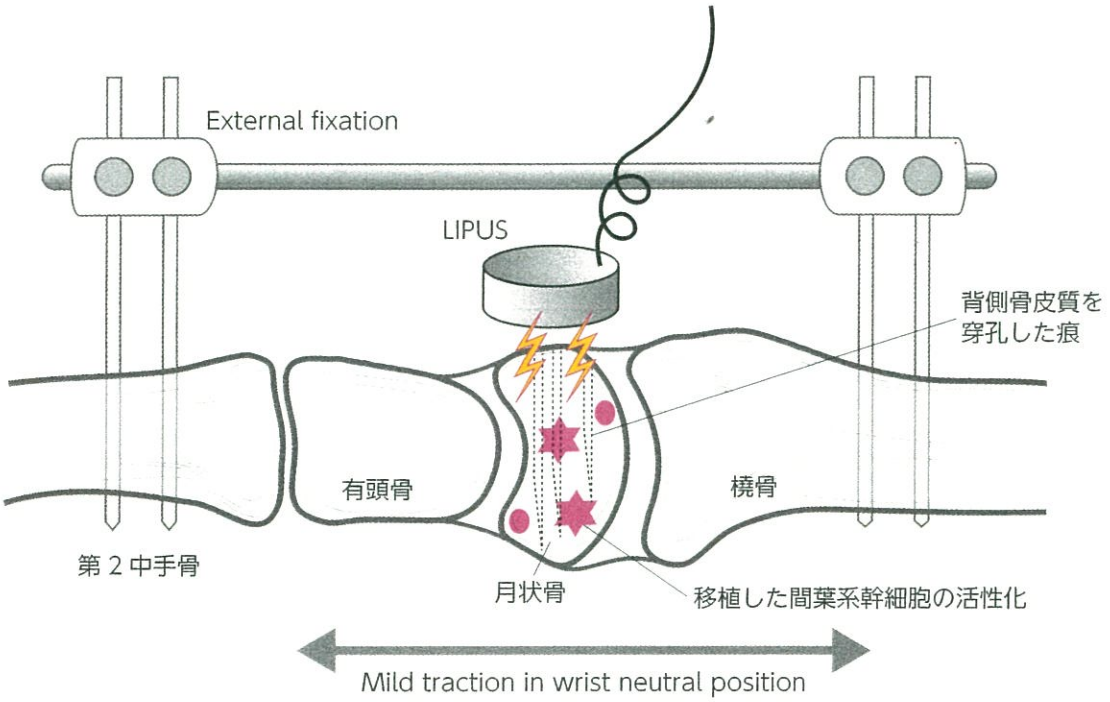


手関節掌背屈中間位，軽度牽引した状態で固定する。8週間で抜去

成績

手術時年齢は15～77歳(平均44.0歳)，経過観察期間は12～194カ月(平均50.45カ月：4.2年)であった。創外固定ピンの感染は7例認めたが，いずれも抜去にて改善した。追加手術はstageⅢAとⅢBの症例で1例ずつであり，いずれも部分手関節固定(Graner法)を行った。Mayo wrist scoreは，excellent 9例，good 29例，fair 8例，poor 5例であった。Poor 5例のみ術後に疼痛が改善しなかったが，stage Ⅲ/ⅡA/ⅢBの順に1/1/3例と病期には依存していなかった。単純X線像にて，CHRは術前平均0.52から術後平均0.51となり，ほぼ不変で有意差はなかった。SIは術前平均0.37から術後平均0.31へと有意に低下した。最終評価時の単純X線Lichtman分類は，術前stageⅡは12例中10例で進行を認め，stageⅢAは25例中8例で進行した。StageⅢBの14例はそのままであった。

図6 創外固定＋LIPUS



LIPUSは３カ月間行う

MRIを評価できた症例は50例であり，Ogawa's gradeは術前grade 3～5(平均4.55)から術後grade 1～5(平均3.30)へと有意に改善した($p<0.001$)。Grade 1または2と著明な改善例は18例(36%)，部分的な改善例を含めると31例(62%)であった。一方，不変または悪化した症例も19例(38%)みられた。特にstageⅢBでは，著明な改善例は14例中2例のみであった。

症例提示

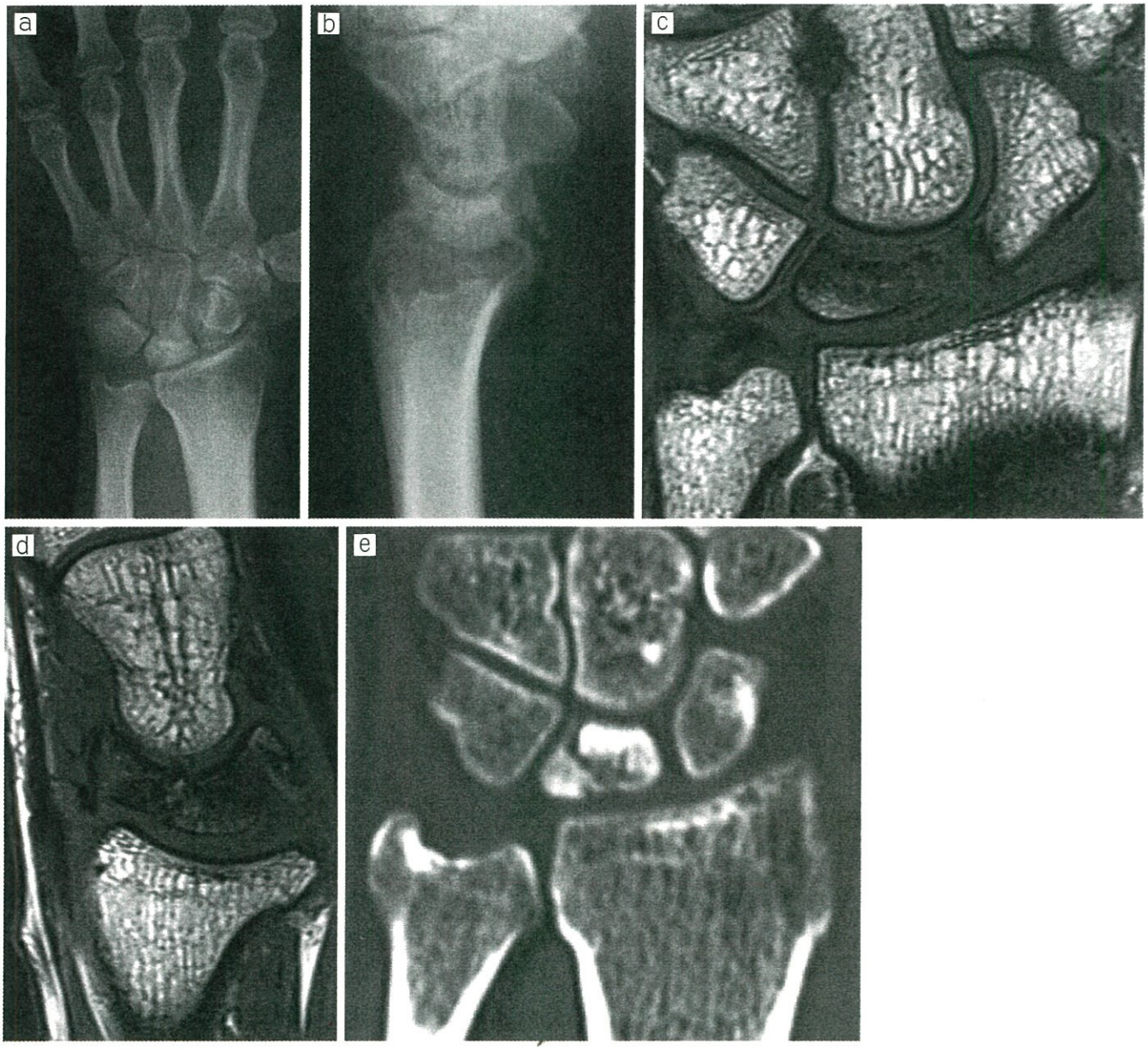
患者：35歳，男性
主訴：左手関節痛
現病歴：腕立て伏せでバランスを崩してから左手関節痛が出現し，農業資材の取り扱いという手を酷使する仕事においても支障をきたした。半年間の保存治療に抵抗性であり，紹介受診となった。
身体所見・検査所見：左手関節背側はびまん性に軽度腫脹し，中央に圧痛を認めた。動作時痛を認め，可動域は背屈40°，掌屈10°，握力は右46kgに対し，左は19kgで痛みを伴った。単純X線像では，月状骨は軽度圧潰を認め，CHR 0.57，SI 0.36，radioscaphoid angle(RS角)61°で，Lichtman分類はstageⅢBであった**(図7a，b)**。MRI画像では，月状骨がプロトン強調像，T2強調像ともに全体に低信号を呈したが，プロトン強調像にて部分的に等信号の領域も認め，Ogawa's grade 4であった**(図7c，d)**。CT画像において，月状骨の粉砕や分節化は軽度であったため**(図7d)**，自己骨髄血移植治療を行う方針とした。
手術：前述のように行い，移植骨髄血は腸骨より採取した。
術後経過：術後8週で最近位のピンに軽度の感染を認めたが，ちょうど抜去する時期であり，抜去後の感染悪化は認めなかった。術前の痛みは術後早期から改善し，創外固定を抜去後にも痛みが強まることはなかった。術後3カ月から徐々に元の仕事を再開し，術後6カ月で完全に復帰した。術後6年，疼痛はなく，左手関節可動域は背屈70°，掌屈60°，握力は45kg(健側比93%)，Mayo wrist scoreは90点(excellent)であった。Disabilities of the arm, shoulder and hand(DASH)scoreは0点

である。単純X線像では，CHR 0.57，SI 0.31，RS角63°と，軽度の圧潰進行を認めるも，Lichtman分類はstageⅢBのままであった(**図8**)。MRI画像は，術後に中央部の分節化が進行しているように見えるが，掌背側を中心に部分的に信号回復を認め，術後6年でも回復傾向にあり，Ogawa's gradeはgrade 3である(**図9**)。

適応

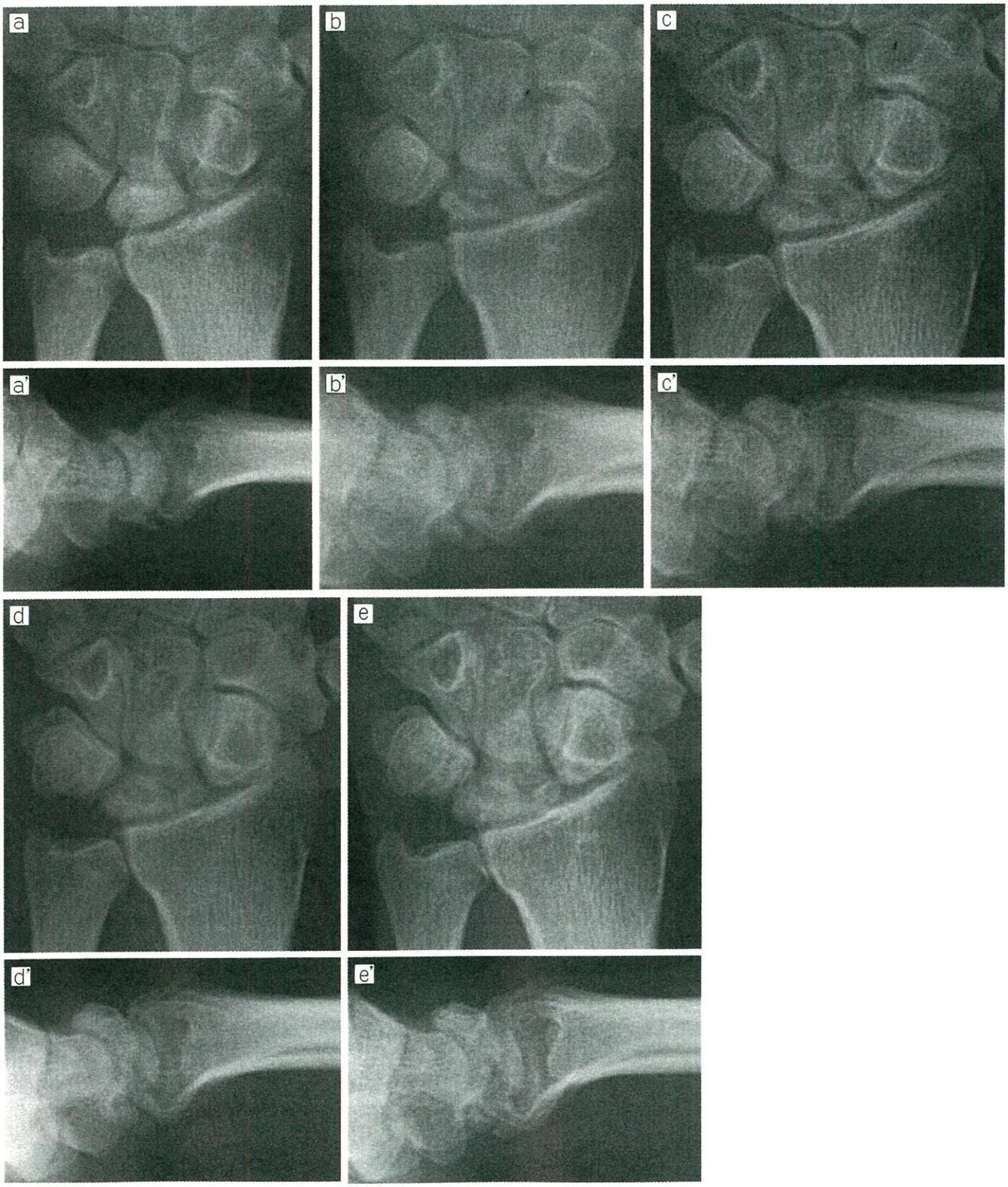
本法を行うと月状骨は軽度圧潰することが多いが，潰れることは悪いことだろうか。この答えを見つけるべく筆者ら[8),10)]が行った動物実験を紹介する。まず，皮質骨と軟骨で囲まれた月状骨に類似した壊死骨モデルとして，ウサギの第4足根骨を用いた。約1cmの立方形に近い形をしており，

図7　症例の術前画像所見



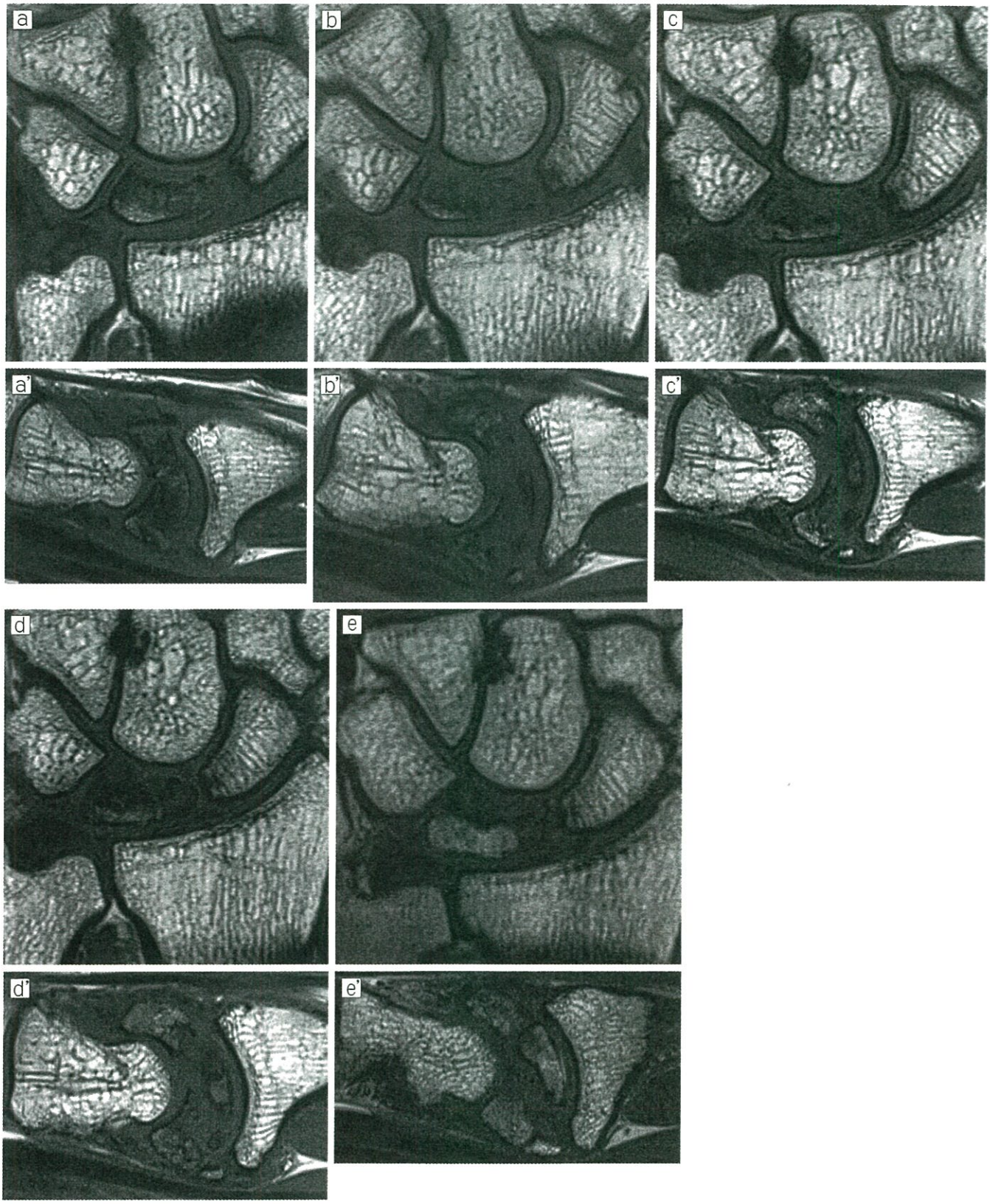
a：単純X線正面像
b：単純X線側面像
c：MRIプロトン強調冠状断像
d：MRIプロトン強調矢状断像
e：CT冠状断像

図8 症例の術後単純X線所見



a～e：正面像
a'～e'：側面像
a, a'：術前
b, b'：術後1年
c, c'：術後2年
d, d'：術後3年
e, e'：術後6年

図9 症例の術後MRI所見

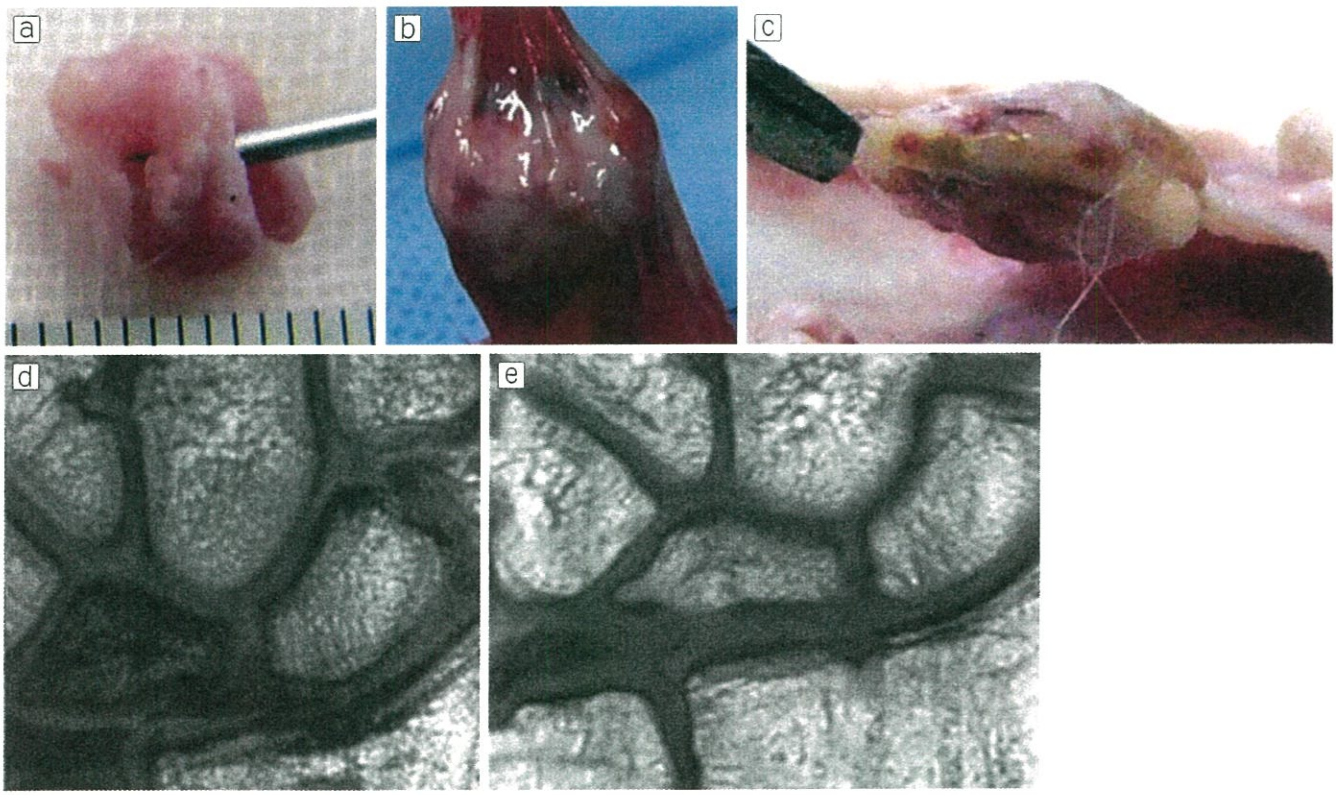


a～e：プロトン強調冠状断像
a'～e'：プロトン強調矢状断像
a, a'：術前
b, b'：術後1年
c, c'：術後2年
d, d'：術後3年
e, e'：術後6年

周囲は軟骨と皮質骨で覆われているという点で月状骨類似モデルとした。液体窒素に5分間浸した後，4つの群(コントロール群，ドリリングのみ行ったドリル群，末梢血を移植した群，骨髄血を移植した群)に分け，背部皮下に埋没させた。12週後の肉眼所見が非常に特徴的で，骨髄血を移植したものはドリリングや末梢血を移植したものと明らかに異なり，原型を留めないほどに赤色調に扁平化していた。組織学的に見てみると，骨髄血移植群のみ新生骨が豊富で，皮下という環境に合った形に潰れてはいるものの骨活性は認められた。このことから，「潰れること」つまり「軟化すること」は，壊死骨再生の結果であると考えられる。自家骨髄血移植は，橈骨短縮術や有頭骨短縮術といったいわゆるleveling手術ではなく，力学的な環境は変えていない。つまり，月状骨は元からの置かれた環境に順応する形になり骨再生したと考察する(**図10**)。また，本法で追加手術を要したうちの1例は，術前の粉砕が強く分節化をきたしていた。Bainら[12]が報告した関節鏡所見による分類からもわかるように，月状骨が軟化または分節化していても，軟骨面は連続性が保たれている症例もみられる。そのような症例であれば，月状骨背側骨皮質のみ穿孔し，骨髄血を月状骨内に染み渡らせるように注入することで，壊死骨の再生が期待できるが，軟骨面も含めて完全に分節しているような症例には，効果不十分といわざるをえない。

以上から，本法の手術適応は，Lichtman分類stageⅡはよい適応と考えられ，stageⅢA，ⅢBも粉砕や分節化が少ない症例は適応といえる。

図10　動物実験と臨床像の比較



壊死骨に対して骨髄血移植を施行。① 移植細胞は，壊死した骨梁を足場として増殖，② 骨吸収，骨形成が起こり，③ 環境に順応した形態に骨再生する
a～c：家兎立方骨
a：骨髄血移植前
b：骨髄血移植4週
c：骨髄血移植12週
d，e：Kienböck病の月状骨MRI画像
d：術前
e：術後

現在，本法の発展型として，分節化の強い症例には，骨釘移植を追加することで対応しており，今後報告していく予定である。

終わりに

Kienböck 病の病態は特定の1つの要因というよりは，複合的な要素が関与することがわかってきている。手術治療方法は，数多く報告されているが，その病期や患者の状態に応じた手術方法を採用すべきである。その際，too much な手法ではなく，より低侵襲で簡便な方法を選択すべきである。その理にかなう方法として，本法は選択肢の1つになりうると考えられる。今後は症例の蓄積とともに，長期経過例のまとめも報告していくことを考えている。

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特集：局所麻酔で行える手外科手術のコツとピットフォール

母指手根中手(CM)関節症に対する関節鏡視下滑膜切除術

小川　健*

Key words：母指手根中手関節症(arthritis of carpometacarpal joint of thumb)，関節鏡視下滑膜切除術(arthroscopic synovectomy)，局所麻酔(wide awake surgery)，低侵襲手術(less invasive surgery)

Abstract　母指手根中手(CM)関節症に対する関節鏡視下滑膜切除術の手術適応や基本手技について解説する．手術適応は，母指CM関節の不安定性が少ないこと，ステロイド注射が有効であること，の2つを同時に満たすことである．これは痛みの首座が関節滑膜炎にあることを証明するものである．局所麻酔で行う際のコツの一つは，手根管ブロックを併用することであり，母指牽引時痛の軽減を図っている．手術手技は決して簡単とはいえず，まずは同じく1.9 mm鏡を使う手関節鏡手技に習熟することが大事である．母指CM関節症に対する外科的治療における本術式の位置づけとしては，関節形成術や関節固定術といった手術に代わるものではなく，あくまでそれらの前段階の治療とでもいうべき方法と考えている．しかし，手技の洗練や適応症例の検討が進めば，最終治療手段となりうる可能性もある．

緒　言

母指手根中手関節(carpometacarpal joint of thumb；以下，母指CM関節)は，手指の中では変形性関節症を呈することが多い関節であり，手術治療としては，関節固定術または関節形成術が広く行われ，良好な成績が報告されている[1)~3)]が，いずれも手術侵襲は大きい．一方，変形性膝関節症に対する関節鏡視下滑膜切除術は効果が少ないとされ[4)]，現在はほぼ行われていない．しかし，関節の安定性が高い股関節では，軟骨破壊の進行を遅延させたという報告もある[5)]．また，手指に関しては，非荷重関節であり，不安定性の少ない母指CM関節であれば，関節滑膜を物理的に切除することは，関節内圧の減少と関節症性変化の進行予防という点で有益であると考えられる[6)7)]．初期の母指CM関節症に対する関節鏡視下滑膜切除術の報告は散見されるが[8)]，進行期に対しての報告は我々の先行研究のみである[9)~11)]．本稿では，本法の実際を紹介し[12)]，手術の際のピットフォールを解説するとともに，治療成績をまとめ，今後の展望も含めて考察する．

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手術適応

術前単純X線Eaton分類[13)]に関係なく，母指CM関節の不安定性が少なく，母指CM関節内ステロイド注射に効果を示すが再燃してしまう症例

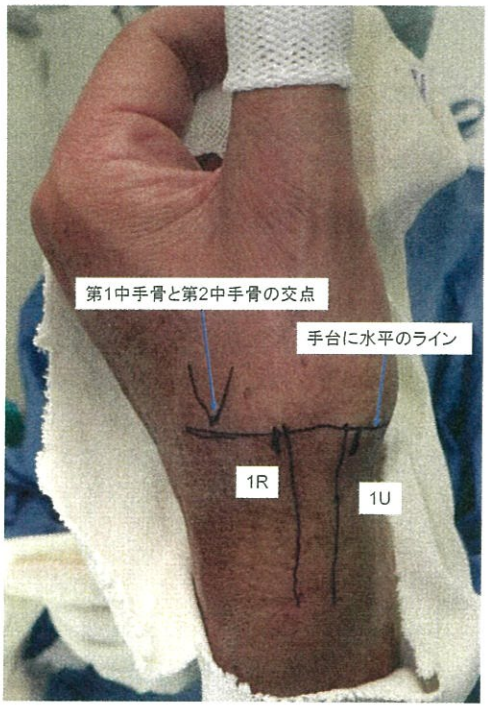


図 1. ポータルのランドマーク
目安は，第1中手骨と第2中手骨の交点である．このポイントをランドマークとし，水平のラインを引いておく．すべてのポータルはこのライン上に置かれることになる．

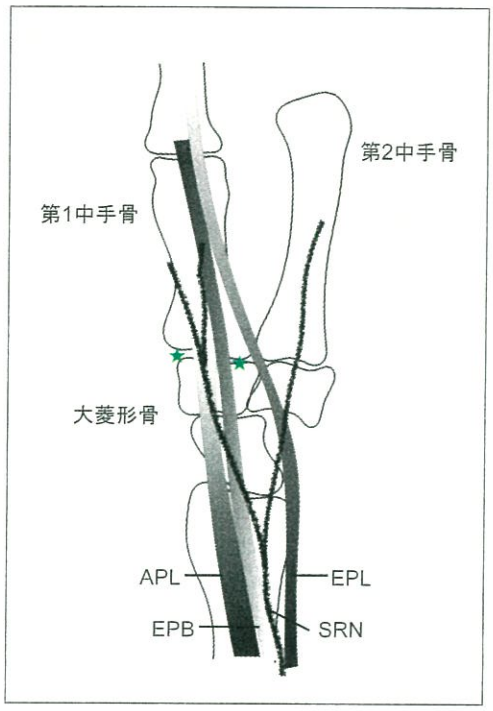


図 2. ポータルと腱・神経の位置関係
橈骨神経浅枝(superficial branch of radial nerve：SRN)は，長母指外転筋(abductor policis length：APL)と短母指伸筋(extensor policis brevis：EPB)の直上を走行するため，水平のライン上でAPL，EPB(1st compartment)の両サイドがポータルの位置となる．
EPL：extensor policis longus

としている．

手術の実際

1．セッティング

母指にフィンガートラップを装着し垂直牽引とする．当院は牽引台を用いて10ポンドを目安に牽引をかけているが，牽引台がない施設では，上腕部を手術台に固定し，牽引量は垂直方向への高さで可及的に調整を図れば良い．

2．麻　酔

基本的には局所麻酔で行っており，以下の3つを併用する形をとっている．

① 手根管内ブロック
② 橈骨神経浅枝ブロック
③ ポータル部分の局所ブロック

まず手根管内に1%キシロカイン5 m*l*で正中神経ブロックを行い，次にエピネフリン含有1%キシロカイン5 m*l*で橈骨神経浅枝ブロックを行う．ポータル部(1R，1U，thenarポータル)は，1%キシロカインがそれぞれ1 m*l*も入れば十分である．

3．ポータル作成

目安は，第1中手骨と第2中手骨の交点である(**図1**)．このポイントをランドマークとし，水平のラインを引いておく．すべてのポータルはこのライン上に置かれることになる．橈骨神経浅枝(superficial branch of radial nerve：SRN)は，長母指外転筋(abductor policis length：APL)と短母指伸筋(extensor policis brevis：EPB)の直上を走行するため，水平のライン上でAPL，EPB(1st compartment)の両サイドがポータルの位置となる．1st compartmentの橈側が，1Rポータル，尺側が1Uポータルである．1Uポータルの尺側には長母指伸筋(EPL)が走行するため，こちらも目安の一つとなる(**図2**)．さらに排液用ポータルとして，掌側にthenarポータルを追加する．こちらは排液のみに利用するため18ゲージ針を挿入

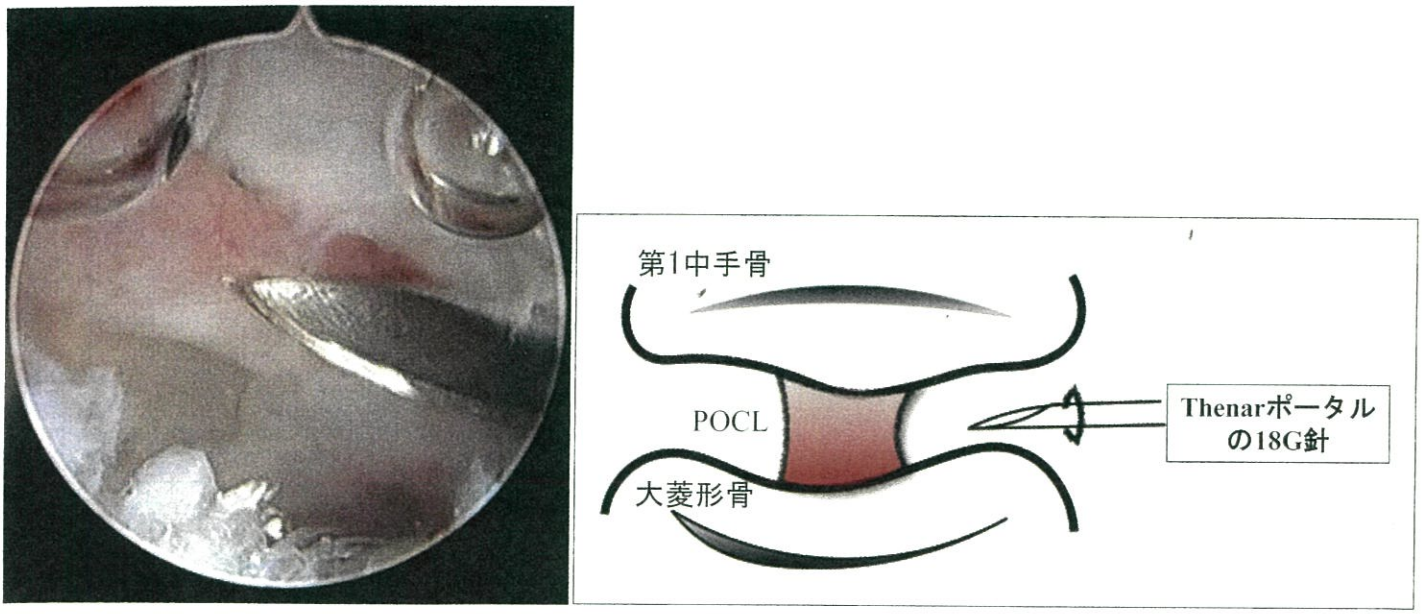
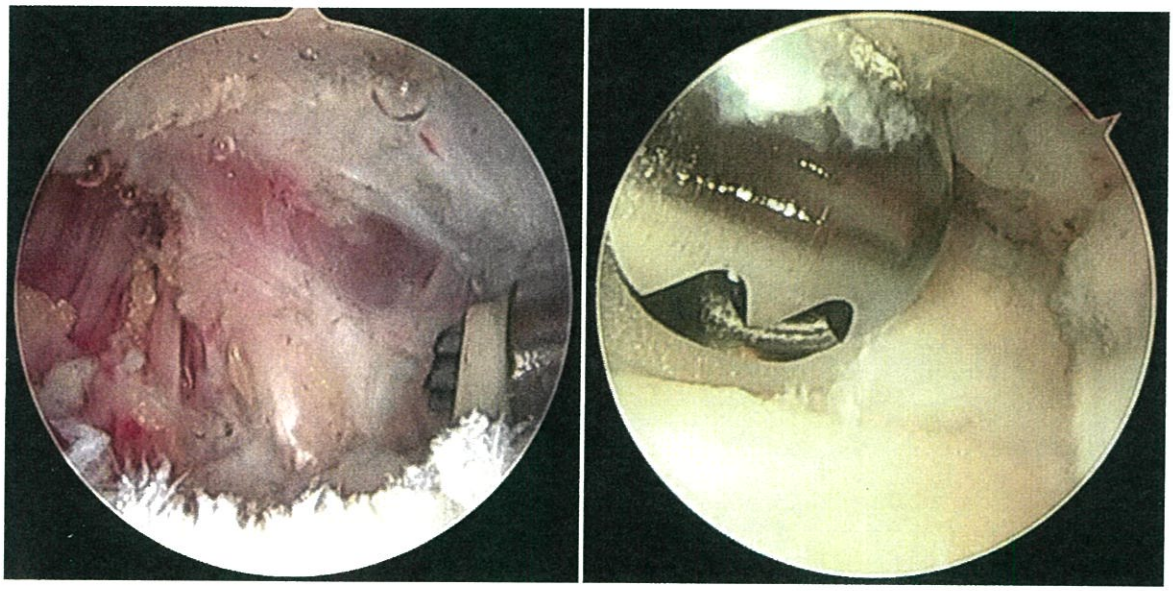


図 3. 関節鏡による関節内所見とシェーマ
掌側手根中手靱帯(palmar oblique carpometacarpal ligament：POCL)



a | b

図 4.
a：アルスロケア
b：シェーバー．関節鏡を適宜交替しながら滑膜切除を進める．

する．あまり手関節の中央に寄り過ぎると正中神経があるので注意する．

4．滑膜切除

直径1.9 mm，30°斜視鏡(Stryker Co. Ltd. or Smith & Nephew Co. Ltd.)を使用する．画面の上に第1中手骨，下に大菱形骨が見えるように画面を調整する(**図3**)．シェーバー(Stryker Co. Ltd.)やアルスロケア(Smith & Nephew Co. Ltd.)を用いて，関節鏡と適宜ポータルを替えながら操作を進める(**図4**)．滑膜とともに遊離体があれば切除するが，関節軟骨の掻爬や穿孔は行っていない．関節包や靱帯がしっかり見えるまで滑膜切除を行うよう心がける．特に掌側手根中手靱帯(palmar oblique carpometacarpal ligament；以下，POCL)の周辺に炎症性滑膜が存在することが多く，POCLがしっかりと見えるまで滑膜を切除する(**図5**)．POCLは母指CM関節の安定性に最も重要であるため，滑膜とともに損傷すると，術後の不安定性を惹起しかねないため注意を要する．

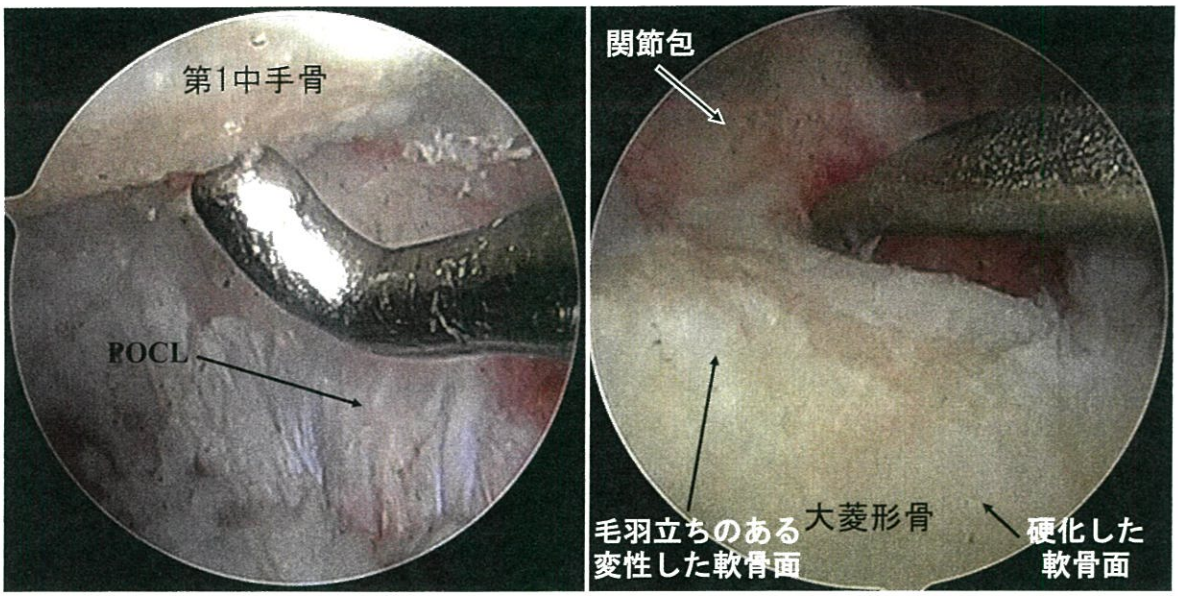


図 5. 滑膜切除後の状態

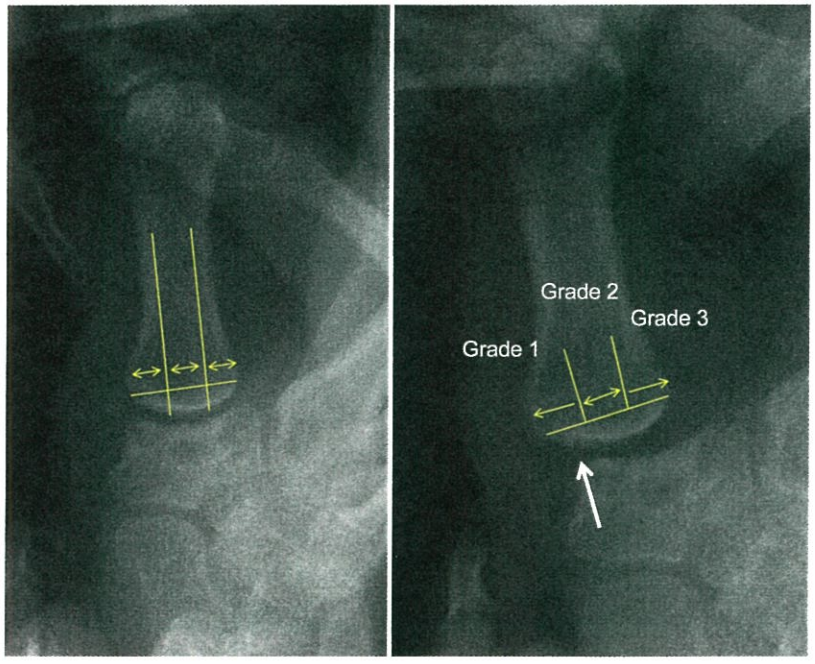


図 6.
X 線透視正面像
徒手的に第 1 中手骨に橈側ストレスをかけ，大菱形骨の橈側縁からどの程度移動するかをみる．第 1 中手骨関節面を 3 等分して，不安定性を Grade 1～3 で評価する．

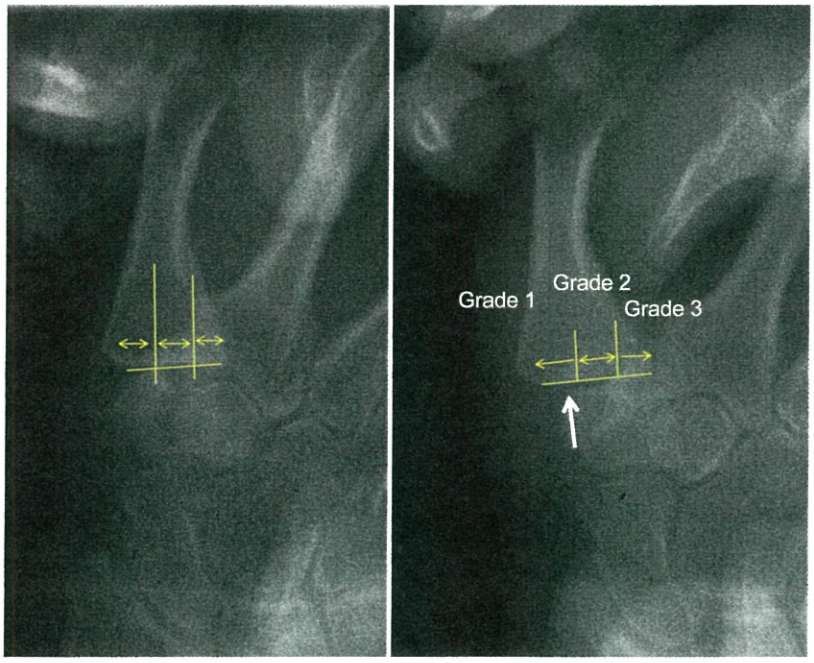


図 7.
X 線透視側面像
徒手的に第 1 中手骨に背側ストレスをかけ，大菱形骨の背側縁からどの程度移動するかをみる．第 1 中手骨関節面を 3 等分して，不安定性を Grade 1～3 で評価する．

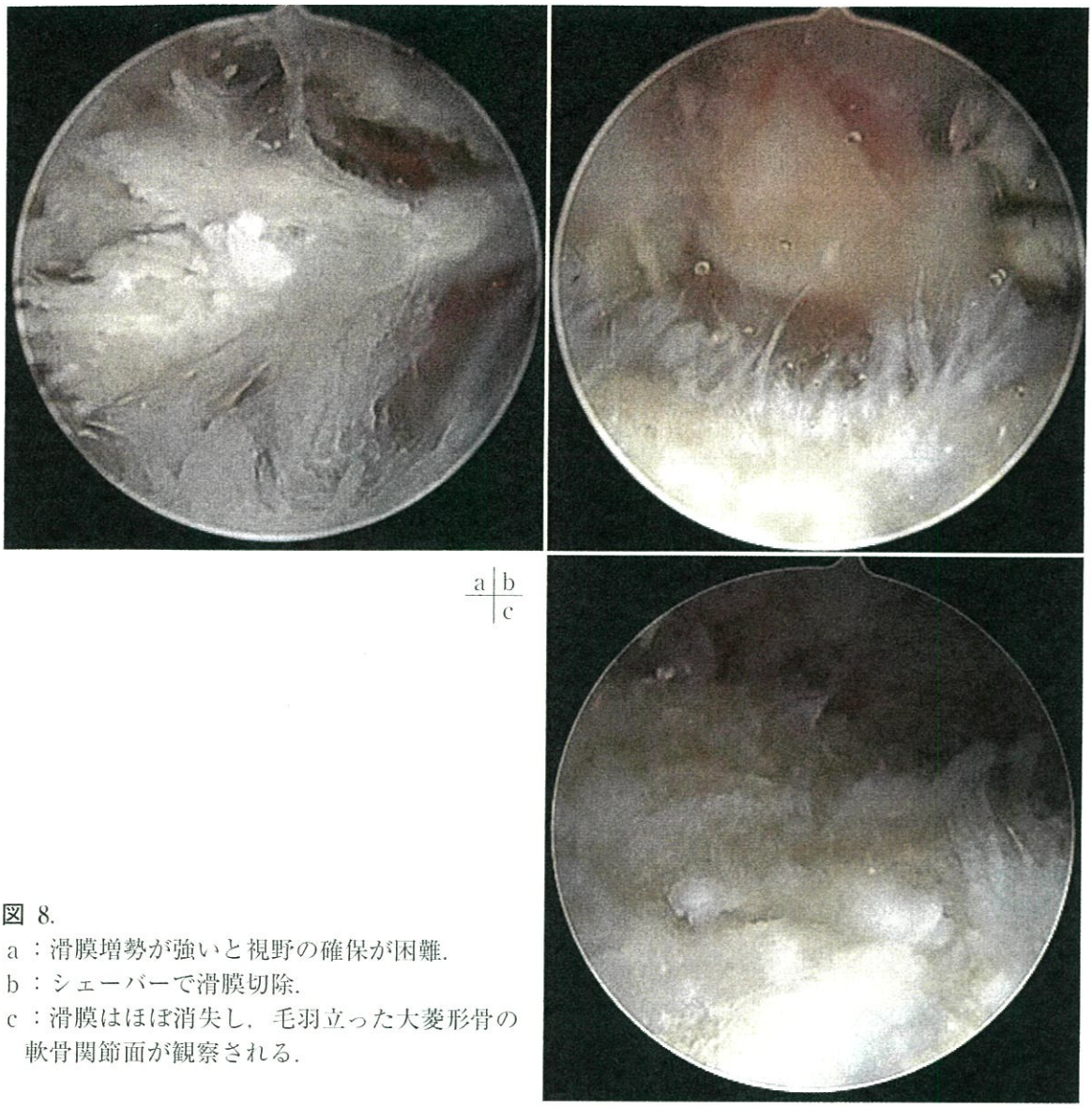


図 8.
a：滑膜増勢が強いと視野の確保が困難.
b：シェーバーで滑膜切除.
c：滑膜はほぼ消失し，毛羽立った大菱形骨の軟骨関節面が観察される.

5．外固定

術後の外固定は，Thumb spica シーネとし，原則2週間行う．しかし，動作時痛が続く症例も多く，適宜装具やスプリント(術前の保存治療で使用していたもの)などを併用している.

ピットフォール

1．手術適応

独自に作成した基準(**図 6, 7**)で，徒手ストレステストにて不安定性を評価し，Grade 1 の症例のみを本法の適応としている．初期の症例で Grade 2 が1例含まれており，疼痛 VAS は術前 100 から術後 19 に改善したが，DASH が術前 51 から術後 65 に悪化している.

2．セッティング

垂直牽引で行う際，上腕部にうまくカウンターがかからないと関節のスペースを確保できない．上腕遠位 2/3 辺りにベルトが位置するように手台に括りつける.

3．麻　酔

当初は，ポータル位置と橈骨神経浅枝ブロックのみで行っていたが，術中にフィンガートラップで牽引している母指全体に痛みが出て，手術の継続が難しかった症例を経験した．そこで手根管内での正中神経ブロックを追加するようにしたところ，牽引による痛みの訴えはなくなった．また，手技に慣れるまでの数例は，全身麻酔，伝達麻酔下に実施することも考慮しても良い.

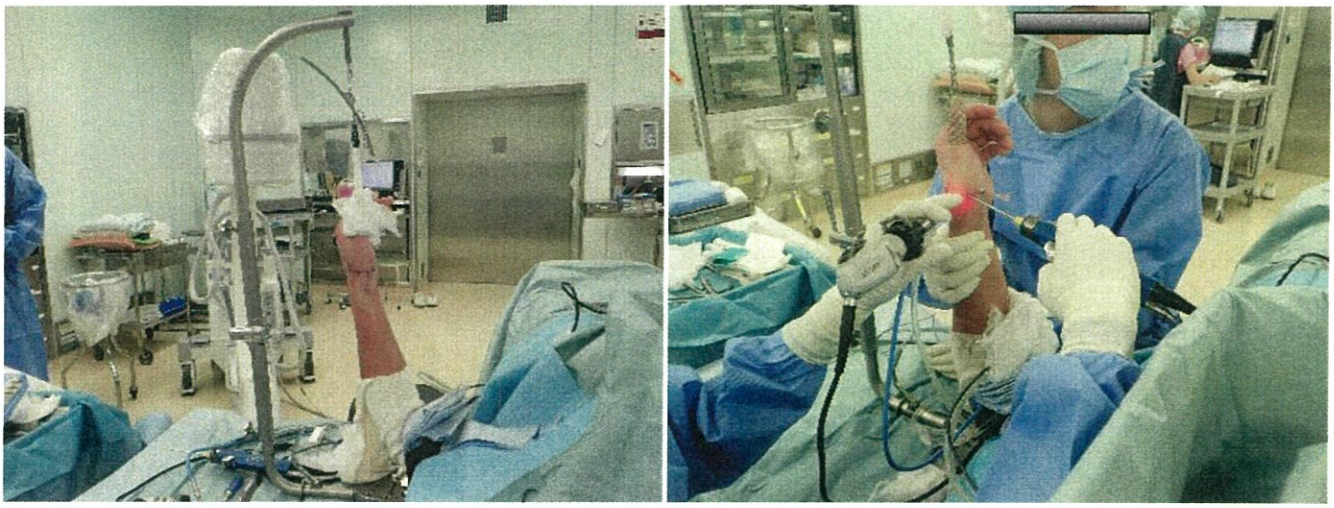


図 9.
a：最初のうちはX線透視を準備.
b：助手は手関節を回外させた位置でキープする.

a | b

4．手術手技

(1) 母指CM関節は，working spaceが狭く，滑膜増勢も強いことが多いため，手技的には簡単とはいえない(**図 8-a**)．まずは同じく1.9 mm鏡を使う手関節鏡手技に習熟することが大事で，少なくとも50例，できれば100例以上の手関節鏡手術の経験が望ましい．手関節鏡手術が必要となる症例は，通常そこまで多くないが，筆者自身は，橈骨遠位端骨折手術の際に併用していたため，母指CM関節鏡も大きな抵抗なく入っていくことができた．

(2) 慣れるまではX線透視を併用し，関節鏡の位置を確認したほうが安心である(**図 9-a**)．実際に舟状大菱形骨(ST)関節に入っていたということも経験している．関節面のカーブがCMとSTで全く異なるので，慣れればすぐに違うことがわかるが最初は難しい．

(3) 術者は患者の頭側に立ち，助手は手関節を回外させた位置でキープする．単純に母指を垂直牽引した安静姿位だと手関節はほぼ中間位となるため，母指の橈側から行う操作が全くできない．助手に手関節の回外位をキープするように指示することが大事である(**図 9-b**)．

(4) 関節鏡とシェーバー，アルスロケアを適宜入れ替えながら滑膜切除を進めると(**図 8-b**)，関節内spaceが確保され，視野も器具の出し入れも容易となってくる(**図 8-c**)．

5．後療法

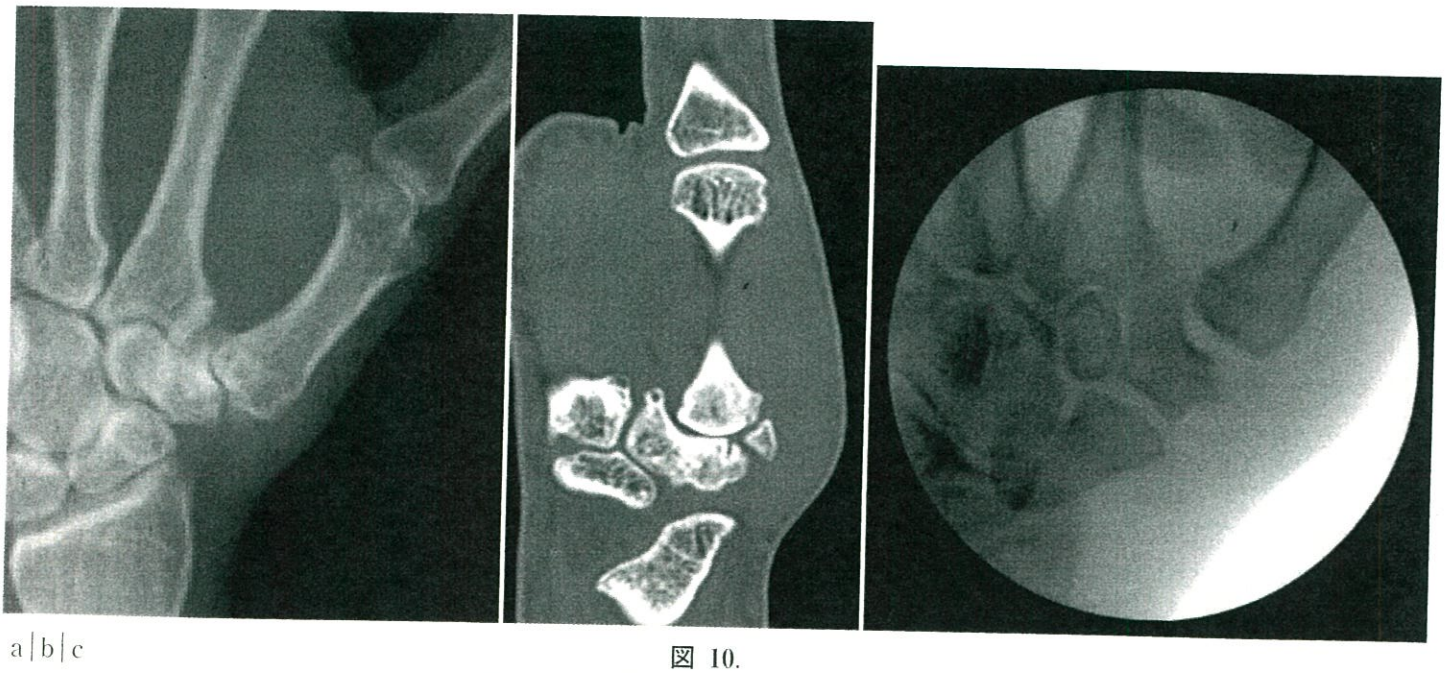
2週間の外固定除去後も，2か月程度は可能な範囲で安静を指示し，仕事の際は適宜装具を装着させる．また腫脹が持続する症例には，NSAIDや漢方薬(治打撲一方など)の内服を継続させることもある．

【代表症例】 35歳，男性．漁業に従事され，1年ほど前から左母指痛が出現した．母指CM関節の不安定性はなく，関節内ステロイド注射は効果があるも一時的であり，2回再燃を繰り返した．Eaton分類はStage 3で，関節内遊離体を認めた(**図 10**)．手術は局所麻酔下に行い，関節鏡下滑膜切除に加えて，遊離体を摘出した．術後1か月で，痛みは軽減傾向にあり(**図 11**)，術後1年qDASHは0，VASは術前100が術後20と改善し，術前同様の漁業に復帰されている．

治療成績

1．対　象

手術適応の条件に合致し，術後6か月以上経過観察できた39例41指(男性5指，女性36指)を対象とした．術前単純X線(Eaton)分類は，Stage 2 13指，Stage 3 26指，Stag 4 2指であった．評価は，visual analogue score(VAS：100点満点)，DASH，可動域，ピンチ力，単純X線について，術前後で統計学的に比較した．また術後満足度を5段階(大変満足1，満足2，どちらともいえない



a | b | c

図 10.
a：術前 Eaton 分類 Stage 3.
b：CT にて遊離体を確認できた.
c：不安定性テストでは安定しており，Grade 1.

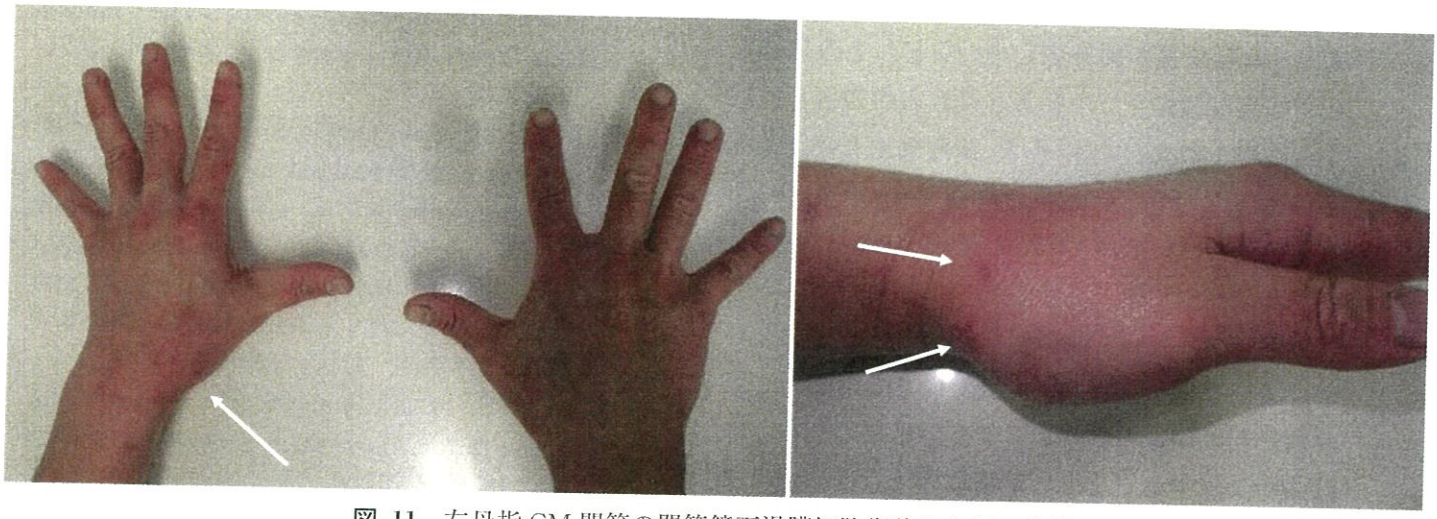


図 11. 左母指 CM 関節の関節鏡下滑膜切除術後 1 か月の状態
ごく軽度の腫脹が残るも，創は目立たず痛みも軽減傾向にある.

3. 不満足 4. 大変不満足 5)で調査した.

2．結　果

年齢は平均 61.9(35～77)歳，観察期間は平均 30.6(6～87)か月．手術時間は平均 43(28～67)分で，手術に伴う重篤な合併症はなかった．VAS は術前平均 83(53～100)が術後平均 39(0～92)，DASH は術前平均 65.2 から術後平均 39.2 と，術後有意に改善した．可動域・ピンチ力に有意差はなく，単純 X 線で Stage の進行を 4 例に認めたが，著明に悪化した症例は認めなかった．VAS が改善した症例は 33 指(80%)であり，著効した症例(最終評価時の VAS が術前の半分以下)は 25 指(61%)で，うち 10 指は 0 となった．一方，8 指(20%)は VAS が術前と同等であり，うち 5 指(12%)が追加手術となった．患者満足度は平均 1.78(1～3)であり，追加手術となった症例を含めても本法に対して不満足と訴えた症例はいなかった.

3．考　察

41 指の母指 CM 関節症に対して，病期を問わずに関節鏡視下滑膜切除術を行ったが，前述の通り適応条件を 2 つ設けている．1 つ目は母指 CM 関

節の不安定性が少ないこと，2つ目は母指CM関節内ステロイド注射が一度は有効であること，である．母指CM関節症の痛みの原因として，関節滑膜の炎症もしくは関節不安定性が挙げられる[14]．関節内ステロイド注射が一時的にでも効果を示せば関節滑膜炎が，無効であれば関節不安定性が痛みの原因であると推測できる．この不安定性については，筆者が徒手的に判断し，不安定性が強い症例は除外したが，定量的な評価は行えていない．

母指CM関節症に対する関節鏡視下手術は，国内でも散見される．大菱形骨部分切除術にSuture button suspensionplastyを併用した関節形成術[15][16]，APL半裁腱を用いた関節鏡視下関節形成術[17]，関節鏡視下関節固定術[18]など，その良好な術後成績が報告されている．これらの報告と比較すると我々の41指の結果は，除痛効果という意味では劣っているといえる．疼痛VASがゼロになる症例は10指(24%)であり，8指(20%)は術前と変わらない．一方，局所麻酔のみで完遂できるという点においては，骨軟骨に対する操作をしない関節鏡視下滑膜切除術が有利といえる．また，患者満足度については，非常に高い結果であった．除痛効果が少なくとも，手術に伴う合併症がほぼないことがその要因と考えられる．また術前にしっかりと病態と本術式の意味を説明し，ご納得のうえで手術を受けて頂けたため，多少の痛みが残存している方でも，不満足との回答をされなかったと推察する．

母指CM関節症に対する関節鏡視下滑膜切除術は，海外での報告があり，Furiaは，Eaton分類Stage 1と2の軽症例に対して，関節鏡視下滑膜切除術を行った23例と経過観察のみを行った21例を1年間前向きに調査し，手術群でVAS，DASHともに有意に改善したことを報告し，Stage 1，2に対する関節鏡視下滑膜切除術の有効性を示した[8]．しかし，本研究のごとくStage 3または4に対しても関節鏡視下滑膜切除のみで対処した報告は渉猟し得ない．

今後の展望

他の関節鏡視下手術と比較して，疼痛改善が不十分とはいっても約1/4の症例は疼痛がほぼ消失している．現段階では，年齢や性別，術前単純X線Stageや骨棘の大きさ等，有意に成績不良を示す要因は見出せていない．今後，成績不良因子の解明を進め，適応症例を限定できれば，非常に有効な方法になりうると考えている．

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上腕骨遠位端骨折に対する A.L.P.S. Elbow Plating System™ の治療成績

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The outcomes of treatment for distal humerus fracture using A.L.P.S. Elbow Plating System™

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上腕骨遠位端骨折に対する A.L.P.S. Elbow Plating System（以下 ALPS plate）の治療成績について，6 か月以上経過観察可能だった 19 例を対象に検討した．平均年齢は 66.7 歳．全例肘関節後方より展開し，C2・C3 の 4 例で肘頭骨切りを行い，それ以外は上腕三頭筋内外側からアプローチした．固定方法に関しては，後外側プレートと内側 CCS で固定した症例が 5 例，後外側プレートと内側プレートが 14 例であった．遠位スクリューは後外側プレートより平均 2.4 本，内側プレートより平均 2.0 本刺入されていた．平均観察期間は 11.8 か月で，全例で骨癒合が得られた．平均可動域は伸展-12.5° 屈曲 124°，MEPS は平均 94.7 点であった．合併症としては尺骨神経障害 3 例，橈骨神経障害 1 例，内側プレートの違和感を 5 例に認め抜釘を行った．高齢者の症例を含めて，良好な臨床成績を得た．

【緒　　言】

成人上腕骨遠位端骨折は，その整復固定が難しい事やその高い合併症率のため，治療に難渋する事が多いが，各種アナトミカルロッキングプレートが導入されて以降，観血的整復内固定術の良好な初期固定性が期待できるようになった[1-3]．一方で，様々な体格や骨形態に対応するには，アナトミカルプレートといえども難しい症例を経験する．個々の解剖学的構造にあった形状を細部まで兼ね備えたプレートシステムの開発が望まれ，またそれにより高い合併症率の軽減にも寄与する可能性がある．我々は上腕骨遠位端骨折に対し A.L.P.S. Elbow Plating System™（Zimmer Biomet, 東京）（以下，ALPS plate）を使用し，その優れた操作性を実感した[4-7]．今回，その術後治療成績と合併症や問題点について検討し報告する．

【対象および方法】

当院にて上腕骨遠位端骨折に対して ALPS plate を使用して骨接合を行い，6 か月以上経過観察可能だった 19 例を対象とした．性別は男性 3 例 女性 16 例で，平均年齢は 66.7（16 ～ 91）歳であった．骨折型は AO/OTA 分類 A2：9 例，C1：6 例，C2：2 例，C3：2 例であった（図 1）．全例肘関節後方より展開し，C2・C3 の 4 例は肘頭骨切りを行い，それ以外は上腕三頭筋内外側からアプローチした．1 例は肘関節の脱臼を認めたため，一時的創外固定後に二期的に手術を行った．固定方法に関しては，後外側プレートと内側 CCS で固定した症例が 5 例，後外側プレートと内側プレートで固定した症例が 14 例であった（図 2）．後療法は 2 ～ 3 週の外固定を行ったが，作業療法士の監視下に術翌日より自動運動を開始した．単純 X 線にて遠位スクリューの本数，骨癒合の有無を調査し，臨床評価として Mayo Elbow Performance Score（以下 MEPS）を用いた．抜釘の有無と術後の合併症についても調査した．

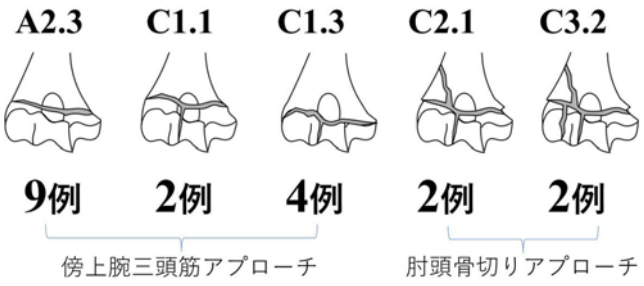

図 1．AO/OTA 分類と手術方法
全例後方アプローチとし，A2，C1 の症例は上腕三頭筋の内外側から，C2, C3 の症例は肘頭骨切りアプローチで行った．

Key words：Ldistal humeral fracture（上腕骨遠位端骨折），anatomical locking plate（アナトミカルロッキングプレート），clinical results（治療成績）

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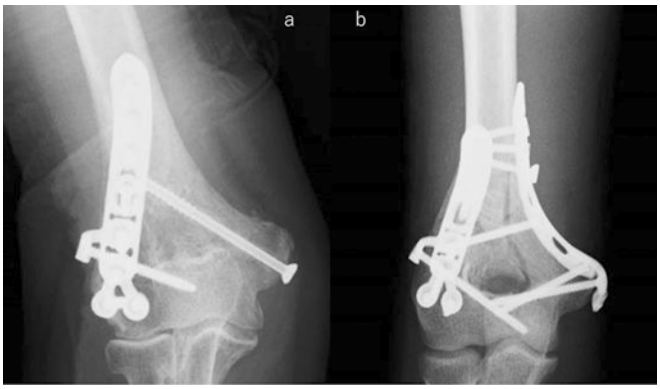


a. 後外側プレート＋ CCS　　b. 後外側＋内側プレート

図2

【結　　果】

遠位スクリューは後外側プレートより平均 2.4（2 ～ 4）本，内側プレートより平均 1.9（1 ～ 3）本刺入されていた（図 3）．平均観察期間は 11.8（6 ～ 20）か月，全例で矯正損失なく骨癒合が得られた．平均可動域は伸展-12.5°（-45 ～ 5），屈曲 124.1°（110 ～ 140），MEPS は平均 94.7（80 ～ 100）点であった．合併症としては尺骨神経障害 3 例，橈骨神経障害 1 例，肘頭骨切り部の Tension band wiring 固定部の術後感染が 1 例であった．内側プレートを使用した 3 例でプレートの違和感を訴え，内 2 例は抜釘を行い改善した．抜釘は，この 2 例に加え，16 歳と 18 歳の 2 症例，計 4 例で行った．

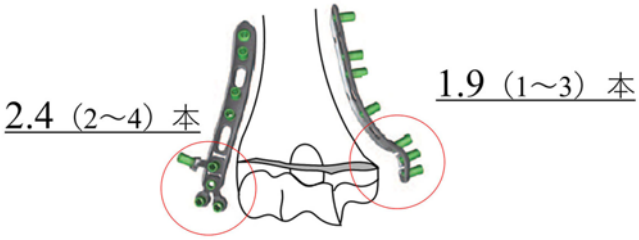
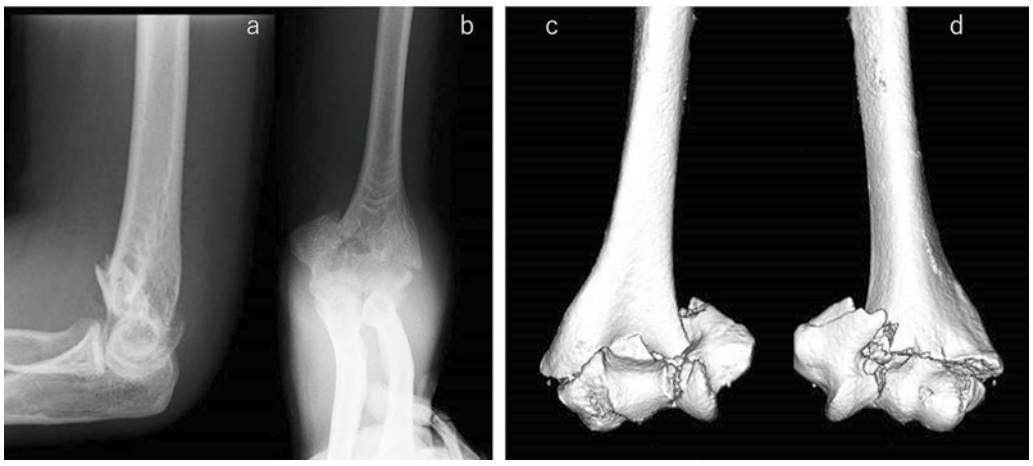


図 3．遠位 Screw の本数
後外側プレートは平均 2.4 本で最低でも 2 本，内側プレートは平均 1.9 本で最低でも 1 本のスクリューが刺入されていた．

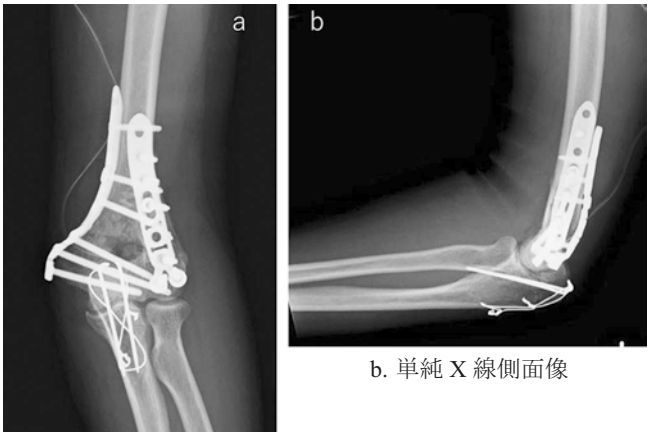
【症例供覧】

症例 1．58 歳女性，風呂場で滑って転倒し，AO/ OTA 分類 C2.1 の左上腕骨遠位端骨折を認めた（図 4）．肘頭骨切りで進入し，後外側と内側プレートで固定し，Locking screw はそれぞれ遠位骨片に 3 本ずつ刺入し得た（図 5）．術後 1 年，左肘可動域は，伸展-15 度，屈曲 130 度で軽度の伸展制限を認めるが，MEPS は 95 点と良好であった（図 6）．



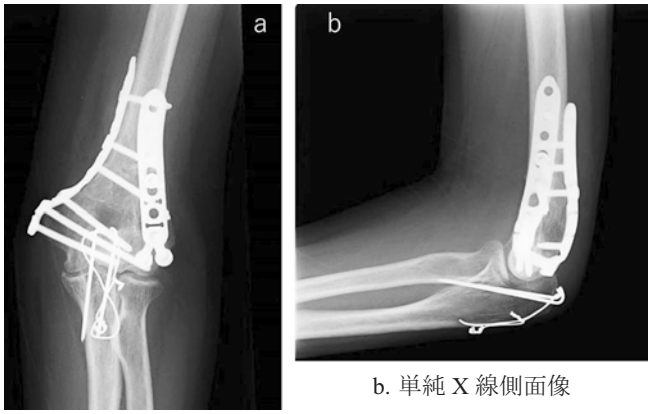
a. 単純 X 線正面像　　b. 単純 X 線側面像　　c. 3D CT（後方視）　　d. 3D CT（前方視）

図 4．症例 1：受傷時
58 歳女性．風呂場で滑って転倒し，上腕骨遠位端骨折（C2. 1）を認めた．



a. 単純 X 線正面像　　b. 単純 X 線側面像

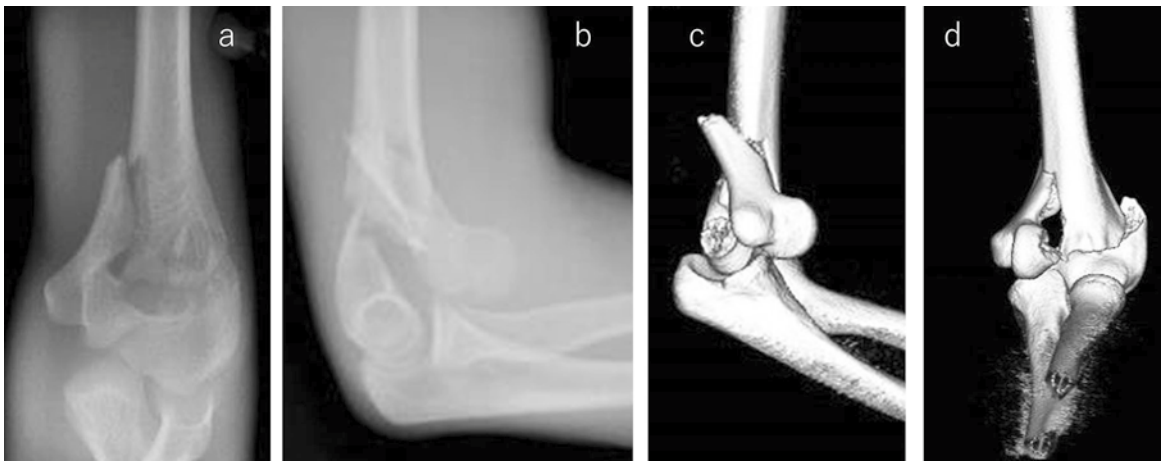
図 5. 症例 1：術直後
肘頭骨切りアプローチで行い，後外側と内外側プレートで固定．それぞれ遠位骨片に 3 本ずつ刺入し得た．



a. 単純 X 線正面像　　b. 単純 X 線側面像

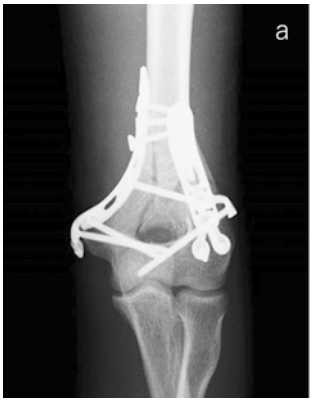
図 6. 症例 1：術後 1 年
伸展 15 度，屈曲 130 度で軽度の伸展制限を認めるが、MEPS は 95 点と良好であった．

症例 2．18 歳男性，少林寺拳法の練習中に転倒し，左肘を受傷した．AO/OTA 分類 C1.3 の上腕骨遠位端骨折を認め，滑車骨片が脱臼した状態であった（図 7）．受傷翌日に後外側と内側の ALPS plate を用いて手術を行った．遠位骨片への Locking screw は後外側に 3 本と内側に 2 本刺入できた（図 8）．術後に橈骨神経の不全麻痺を呈したが，数日で自然回復した．左肘可動域は術後 6 ヶ月で，伸展 0 度，屈曲 140 度であり，MEPS は 100 点であった．痩せ型の体型ということもあり，プレートの違和感が強く，術後 7 ヶ月で抜釘を行った（図 9）．

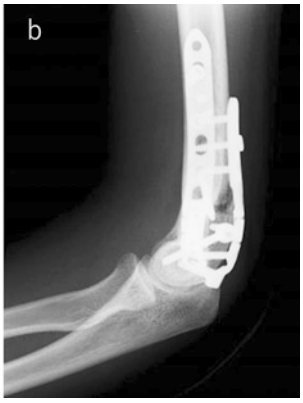


a. 単純 X 線正面像　　b. 単純 X 線側面像　　c. 3D CT（内方視）　　d. 3D CT（後方視）

図 7. 症例 2：受傷時
AO C1.3 で，滑車骨片が脱臼した状態

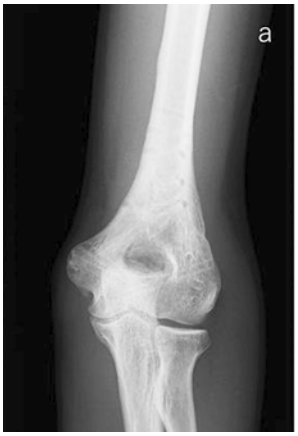


a. 単純 X 線正面像

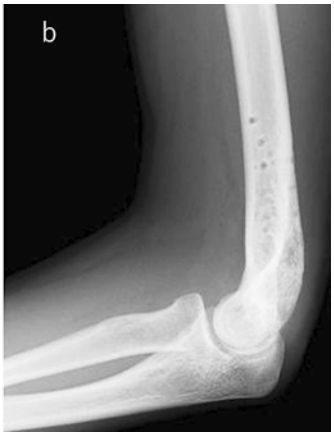


b. 単純 X 線側面像

図 8. 症例 2：術後 2 週



a. 単純 X 線正面像



b. 単純 X 線側面像

図 9. 症例 2：術後 7 ヶ月の抜釘後

【考　　察】

上腕骨遠位端骨折において，内固定の核となる外側顆の固定は，非常に重要である．本研究では，全例後外側プレートを使用し，遠位骨片に最低 2 本，平均 2.4 本の Screw を刺入できていた．本プレートは単軸性ロッキングプレートだが，In situ bending によりプレートをおさえながら方向を調整できるため [4-7]，多くのスクリューで固定できた．また，遠位骨幹部にプレートをスクリュー固定した後でも，顆部スクリューの方向を調整できる．本研究でのスクリューの逸脱は 2 例 2 本のみであり，いずれも肘頭窩へのわずかな突出であった．特に固定性が不安視され，組織の脆弱性が懸念される高齢者の上腕骨通顆骨折でも，多軸性ロッキングプレートと同様に至適位置により長いスクリューを挿入でき，十分な固定性を得ることができる．実際に，後外側・内側プレートともに平均 2 本以上のスクリューが刺入できていた．結果的に高齢者の症例を含めて骨癒合が得られ，良好な臨床成績を得たと考えられた．A.L.P.S Plating system を用いた過去の報告と比較しても我々の術後臨床成績は同等の結果と考えられた（表 1）．骨折型に差があるため単純比較はできないが，特に高田らの報告では全例 AO/OTA 分類 type C に対して使用しており [7]，多彩な骨折型を有する上腕骨遠位端骨折において，様々な状況に対応可能なプレートシステムであると考えられる．

一方で自験例では尺骨神経障害を 3 例（15%）に認めており，本プレートにおいても過去の報告同様に注意を要する問題点と言える．自験例の 3 例を検討すると，C1 が 1 例，A2 が 2 例であり，全例前方移行は行っていなかった．内側プレート 2 例とスクリュー固定が 1 例であり，プレート のみの問題ではない可能性もある．今谷ら，森谷らは最小侵襲尺骨神経移動法を考案し [8-10]，その有用性が期待される．自験例では，最小侵襲尺骨神経移動法を行っていないが，尺骨神経の手術中の愛護的な操作と前方移行が術後障害の予防には大事であると考えられた．

また，症例 2 で起こった術後の橈骨神経障害は大きく転位した骨片による圧迫やその整復固定操作で一過性に生じたものと考えられるが，スクリューが干渉したために生じた医原性橈骨神経障害の報告もある．柳橋らは，内側プレートの設置位置が後方になると，ドリリング操作で橈骨神経を損傷する可能性があるため，手術手技の細部にまで注意する必要があると述べている [11]．

表 1.　ALPS Plate の使用経験に関する報告

著者	症例数	AO/OTA分類 A/C	伸展	屈曲	スコア	尺骨神経障害
加地ら[4]	9	-	-9.7°	131.7°	MEPS 98	1例(11%)
南野ら[5]	17	7/10	-16.4°	120.7°	MEPS 92.9	3例(17%)
高田ら[7]	14	0/14	-14.4°	120.7°	JOA-JEA 88.1	5例(35%)
本研究	19	9/10	-12.5°	124.1°	MEPS 94.7	3例(15%)

本研究の限界としては，比較対象研究ではないことが挙げられる．しかし，手術合併症はALPS plate特有のものではないこと，適切な手技で手術を行えばプレートの種類によらず，骨癒合が得られること[1-3]等より，プレートの機種による優劣はつけ難い．よって，その操作性･固定力を総合的に評価し，機種を選択する訳であるが，ALPS plateはどの骨折型に対しても対応可能であるという点において常に念頭に置くことのできるプレートと言える．

【結　　語】

上腕骨遠位端骨折に対するA.L.P.S Plating systemの治療成績は良好であった．In situ bendingは皮膚障害の低減以外にも，固定性においても有用であった．

この論文は35回日本肘関節学会で発表した．

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編集後記

2023 年度（令和 5 年度）の水戸医療センター研究業績集をお届けします。当院の臨床研究部は 2008 年に設置されたので、16 年目の業績集となります。国立病院機構（NHO ; National Hospital Organization）の病院では、臨床研究部の設置を本部に認めてもらうためには、一定レベルの臨床研究活動実績が必要です。具体的には治験、製造販売後臨床試験、NHO 共同研究、製造販売後調査、競争的研究費、論文発表、学会発表などが研究業績となります。それぞれの研究業績には決められたポイントが付与され、それらを合計した研究ポイントで評価されます。水戸医療センターは 2023 年度（2023 年度が最新データです）の研究ポイントが 635.9 ポイント（2022 年度 692.4 ポイント、2021 年度 790.5 ポイント）でした。臨床研究センターや臨床研究部（院内標榜含む）のある NHO130 病院中、29 位（2022 年度 26 位，2021 年度 27 位）でした。ポイントも順位も下がっているのが残念ですが、頑張っている人は変わらず頑張っているので、研究の裾野を広げることが大切だと感じます。

ポイントの内訳は 1 位、英文論文 198.4 ポイント、2 位、治験新規 185.0 ポイント、3 位、学会発表 109.0 ポイント、4 位、製販後調査公費試験 107.8 ポイント、5 位、競争的資金 14.4 ポイントです。特に治験のポイントは NHO 全病院中 13 位であり、当院の稼ぎ頭です。受託研究実績金額も右肩上がりで、昨年度は 1 億円を突破しました。ポイント獲得領域のトップ 3 は 1 位、心脳大血管 161.6 ポイント、2 位、骨・運動器疾患 77.5 ポイント、3 位、消化器疾患 44.6 ポイント（2022 年度は 1 位、骨・運動器疾患、2 位、泌尿器疾患、3 位、血液疾患・血液がん、2021 年度は 1 位、血液疾患・血液がん、2 位、消化器疾患、3 位、骨・運動器疾患）でした。発表関連の業績は英文論文 32 編、和文論文 9 編、国際学会発表 4 件、国内学会 101 件でした。当院職員が筆頭著者の英文原著論文は 1 編（栗原秀輔医師）、英文レター1 編（堤悠介医師）でした。

今後も職員の研究活動が円滑に進むよう、臨床研究部の活動を継続します。

臨床研究部長　福永 潔