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OPINION REVIEW

COVID-19 and psychiatry training: A cross-national trainee perspective

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Abstract

The coronavirus disease 2019 pandemic has significantly altered many aspects of our professional lives, including how psychiatry as a medical discipline is taught and learnt. Training in psychiatry relies on developing competencies through observing and interacting with patients, developing empathic consultation skills and seeking feedback from colleagues derived from cognitive and constructivist theories of learning, in a time-bound manner. The pandemic has drawn attention to the dual role of psychiatry residents as both trainees and physicians, with a pressing identity crisis at an inopportune time. This paper aims to illustrate some of the emerging themes in psychiatry training during the pandemic and some solutions for the same.

Key Words: COVID-19; Psychiatry; Training; Teleconsultation; Review

Core Tip: There is an urgent need to streamline processes for entry and exit to a psychiatry training program, where it does not exist. Utilizing alternative modes of assessment including anonymized colleague, peer and patient feedback can supplement online assessment tools. Curricular adjustments taking current circumstances into

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account would be well appreciated by trainees. The most important recommendation we propose is provision of formalised intensive training around teleconsultation skills, using simulated scenarios followed by assessment, in addition to guidelines and modus operandi around remote working.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has significantly altered many aspects of our professional lives, including how psychiatry as a medical discipline is taught and learnt. Training in psychiatry relies on developing competencies through observing and interacting with patients, developing empathic consultation skills and seeking feedback from colleagues derived from cognitive and constructivist theories of learning, in a time-bound manner.

The pandemic has drawn attention to the dual role of psychiatry residents as both trainees and physicians, with a pressing identity crisis at an inopportune time. This paper aims to illustrate some of the emerging themes in psychiatry training during the pandemic and some solutions for the same[1].

PROFESSIONAL IDENTITY

Many residents have been expected to assume roles that are not a prescribed part of their specialty training. Further, in some cases residents have also been compelled to acquire skills on the job that were not an expectation when they began residency in psychiatry. While this has resulted in identity crisis in terms of speciality, there is also the additional fear of delay in gaining competencies relevant to psychiatry. Also, due to staff shortages there have been other cases where a premature or an inappropriate delegation of increased responsibility (though within psychiatry) but without the associated privileges including monetary compensation or malpractice indemnity coverage. This results in "Role Confusion", in which a trainee is considered competent to take on a more senior role but actually this may result in a significant delay in their professional development[2]. This is a common theme noted both in both developed and developing countries. In a way, the pandemic has been a masterclass for trainees on practical leadership skills by testing their ability to cope with uncertainty and to make difficult decisions amid heightened anxiety and incomplete information.

CLINICAL SUPERVISION AND DIRECT OBSERVATION

Psychiatry trainees often rely on direct clinical observation and supervision to develop their clinical competencies. This can be an important tool to understanding the complexities of clinical psychiatry. However, this aspect of the training has been significantly compromised during the pandemic. It is currently unclear if virtual means of observation are as effective[3]. However, on a positive note, some residents have reported that the virtual world has opened up and improved lines of communication bringing down the threshold for impromptu teaching or brief ad hoc supervision for specific cases[4].

However, there is a rather unanimous consensus that direct supervision of trainees by psychiatrists has been significantly affected by the pandemic. Trainees seek feedback regarding their interview style, approach, and clinical decision making for which direct observation is imperative. When done virtually, there are inherent problems including difficulty in observing certain subtleties of the mental status examination or non-verbal communication. Also, technological issues like weak internet signals and poor video/audio can compromise on the quality of the interaction[3]. Similarly, wearing personal protective equipment (PPE) adds a physical barrier between trainees and patients that often obstructs observation of facial expressions that can be crucial for a quality assessment[5].

While most of the clinical care transitioned to the virtual format during the pandemic in developed countries, it was more of a challenge in developing countries due to the 'digital divide' characterised by lack of access to quality internet[6]. This also meant that psychiatric training in developing countries was disproportionately affected during the pandemic. Softening of regulations involving tele-mental health *e.g.*, Health Insurance Portability and Accountability Act, 1996 in United States have significantly expanded the scope of virtual care provisions, particularly in developed countries[7].

Also, most of the mental health services in public sector are through teaching hospitals in tertiary centres in developing countries (including South Asia) through self-referral unlike the tiered mental health provisions that exist in developed countries like United Kingdom. Hence, COVID related factors including lock downs and social restrictions are likely to have a disproportionate impact on our patients in developing countries. This also translates to a corresponding disproportionate impact on psychiatric training in developing countries due to the significantly reduced foot fall in tertiary psychiatric institutions, typically located in metro cities (during lockdown periods).

Previous literature emphasises how personalized feedback systems facilitate change. The more subjective perception and experience is assessed and reconsidered, the more significant change can actually take place. Differential steps may be considered to promote motivation, provide more security in disruptive times, and make change possible while supervising trainees. Triangulated research designs and domain knowledge can be considered together with an idiographic assessment of subjective values, subliminal affect perceptions, attitudes, values and beliefs to better facilitate this process[8].

CURRICULAR CHANGES INCLUDING ASSESSMENTS:

In United Kingdom, the Royal college of Psychiatry (RCPsych) has been actively working with the trainees to ensure the quality of training is not significantly compromised and are provided the right support with appropriate leeway (in terms of curricular adjustment) at the same time. With most conferences being cancelled, RCPsych has successfully trialed a free webinar series by experts on different topics including but not limited to COVID-19 related topics. A variety of other organisations have also run several webinars useful for psychiatry trainees. Similar examples from developing countries include different divisions of Indian psychiatric society (IPS) and Psychiatrists association of Nepal (PAN) have been actively running webinar and virtual sessions, more aimed at trainee psychiatrists that have been well received. The local teaching programs have transitioned online in most institutions in all the three countries. In fact, an off shoot of this has been some well received local teaching sessions are now rolled out virtually across institutes or even different nations globally. In United States, the National Neuroscience Curriculum Initiative produced a "quarantine curriculum", which has been well-received by trainees, including lectures ranging from complex trauma, borderline personality disorder to child psychiatry and psychosis[9].

In United Kingdom, at a national level, examinations, including Clinical assessment of skills and competencies (CASC) and appraisal have all moved to virtual platforms [10]. The online CASC exam successfully rolled out recently was possibly the first of its kind globally. Standardized role players and simulation techniques have been successfully utilized for these exams. Plenty of thought and consideration has been provided to provide leeway to trainees in terms of career progression including reduction in number of work-place assessments (WPBA) needed and encouraging pieces of self-reflection (including on coping with complex work environment in the background of COVID-19) in portfolio to compensate in lieu of WPBA's.

Similarly, IPS and PAN recommend utilizing virtual platforms for assessment and examinations. However, it is concerning to note a persisting ambiguity in decisions on entry/exit exams in different institutions in South Asia. It is even more concerning to note a possible delay in completion of the training period for trainees in some of the institutions that results in increase in apprehension among trainees.

Previous literature demonstrates how synergistically combining textbook, e-learning cases and a simulated patient course in psychiatry education can be achieved using a trans-disciplinary case-based blended learning framework. The same framework can be used to conceptualise assessments in mental health competencies as well[11]. The added advantage is that this can be helpful for curricular development and harmonization with corresponding mental health curricula in other institutes/countries. E-case based blended learning approaches can expedite the transfer of declarative knowledge to procedural knowledge in practice *via* fostering the understanding of pathophysiological concepts[12]. Similarly, standardized patients have been successfully utilized in medical education to train students' communication skills and this paradigm can be successfully employed for the purpose of assessments as well[13].

RESEARCH

Psychiatry trainees across the globe are encouraged to utilize this period for honing theoretical research skills and to consider taking up literature reviews on topics of interest in lieu of ongoing research that has been stalled. However, it is worth noting that some of the institutions traditionally mandate a piece of original research (not literature reviews) as a prerequisite for completion of even general psychiatric training. Those trainees who have been the most affected in this regard are those who have already embarked on research that requires patient contact. Hence, exploring other research projects at this critical juncture is proving increasingly stressful for these trainees[14]. In institutes where case series can be considered as research activity, facilitating e-collection of academic cases with a step wise feedback system provides a dynamic platform to link recent basic research to clinical practice and familiarizing students with research questions and the current research approach[15].

PERSONAL WELL- BEING AND PASTORAL SUPPORT:

In United Kingdom, it is heartening to note a number of trainee well-being initiatives including the psychiatrist support service, support from psychiatrists trainee committee and a number of local/regional initiatives including mindfulness-based sessions, pastoral support and peer support. Similarly, IPS and PAN have come out with resources and initiatives to support trainee psychiatrists. This is crucial when viewed from the lens of Abraham Maslow's 'hierarchy of needs' since the basic needs including safety need to be met first before any higher order needs including educational/training needs[16].

This approach also included education about good hygiene habits to prevent cross-contamination, access to PPE, surge planning throughout the health system, childcare arrangement, and housing in case of sickness or quarantine. The most helpful interventions were specific or targeted as opposed to general reassurances. For example, sharing institutional dashboards relating the number of occupied beds, number of COVID-related admissions, and detailed contingency plans helped in maintaining a steady flow of accurate information in a transparent manner.

RECOMMENDATIONS

There is an urgent need to streamline processes for entry and exit to a psychiatry training program, where it does not exist. Utilizing alternative modes of assessment including anonymized colleague, peer and patient feedback can supplement online assessment tools. Past interim assessments can also be used to project the final outcome. Simulated role plays or objective structured clinical examination conducted virtually may be a good method for summative assessment. Trainee's research competencies need to be evaluated considering the unprecedented circumstances, to prevent any unfair disadvantage. Curricular adjustments taking current circumstances into account would be well appreciated by trainees. Standard operating procedures need to be chalked out for the current circumstances to contain trainee's anxiety and apprehension on new modes of working.

The most important recommendation we propose is provision of formalised intensive training around teleconsultation skills, using simulated scenarios followed by assessment, in addition to guidelines and modus operandi around remote working. Involving trainee psychiatrists as active stake holders in the entire process from consultation to implementation as well as providing a uniform and consistent message is likely to significantly improve trainee confidence. Also, making clear the roles and expectations of trainee psychiatrists through open and honest discussions at an individual and collective (organisational) level would be the way forward to allay any anxiety[17].

CONCLUSION

The most important recommendation we propose is provision of formalised intensive training around teleconsultation skills, using simulated scenarios followed by assessment, in addition to guidelines and modus operandi around remote working. Involving trainee psychiatrists as active stake holders in the entire process from consultation to implementation as well as providing a uniform and consistent message is likely to significantly improve trainee confidence. Also, making clear the roles and expectations of trainee psychiatrists through open and honest discussions at an individual and collective (organisational) level would be the way forward to allay any anxiety.

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REVIEW

Current and future of anterior cruciate ligament reconstruction techniques

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Abstract

In recent years, anterior cruciate ligament (ACL) reconstruction has generally yielded favorable outcomes. However, ACL reconstruction has not provided satisfactory results in terms of the rate of returning to sports and prevention of osteoarthritis (OA) progression. In this paper, we outline current techniques for ACL reconstruction such as graft materials, double-bundle or single-bundle reconstruction, femoral tunnel drilling, all-inside technique, graft fixation, preservation of remnant, anterolateral ligament reconstruction, ACL repair, revision surgery, treatment for ACL injury with OA and problems, and discuss expected future trends. To enable many more orthopedic surgeons to achieve excellent ACL reconstruction outcomes with less invasive surgery, further studies aimed at improving surgical techniques are warranted. Further development of biological augmentation and robotic surgery technologies for ACL reconstruction is also required.

Key Words: Anterior cruciate ligament reconstruction; Surgical techniques; Revision surgery; Biological augmentation; Computer-aided surgery

Core Tip: Although anterior cruciate ligament (ACL) reconstruction has offered great benefits, particularly to athletes and physical laborers, there is a great deal of room for

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improvement through technology development aimed at achieving more excellent outcomes and restoring performance to a level equal to or higher than before the injury. The all-inside ACL reconstruction technique is a relatively new, minimally invasive method in which both femoral and tibial tunnels are drilled from inside the joint, and its advantages include less postoperative pain and less bleeding. A new computer-aided ACL reconstruction system with high efficacy needs to be developed.

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INTRODUCTION

The anterior cruciate ligament (ACL), located in the middle of the knee joint, is significantly associated with the stability of the knee. Numerous studies have contributed to the advancement of knowledge and treatment of the ACL, as well as knee surgery. Given the anatomical location and roles of the ACL, the strategies for treating it, and the approaches to researching it, one could say that “all roads of the knee lead to the ACL”. This article discusses current and future trends of surgical treatment for ACL.

Based on the challenges that our predecessors faced, ACL repair is rarely indicated for ACL injury. Instead, ACL reconstruction is usually performed.

In recent years, ACL reconstruction has generally yielded favorable outcomes. This procedure is a minimally invasive arthroscopic surgery involving small incisions, and rarely causes significant complications[1,2]. Therefore, ACL reconstruction has been actively performed for in more and more patients, including young professional athletes as well as middle-aged and older amateur athletes[3-5]. Currently, the number of ACL reconstruction procedures performed in the United States is approximately 200000 per year and is expected to increase further[6,7]. Considering the increasing level of orthopedic treatment in the world, as well as an increase in the number of people who desire a high quality of life that permits a high level of activity, there is no doubt that the number of ACL reconstruction procedures will increase.

Nevertheless, ACL reconstruction requires about 6 mo to return to sport after surgery. Consequently, high school and college athletes, as well as professional athletes, often end up stepping down as a player without a complete comeback after undergoing ACL reconstruction because their time as a player is limited. Even after returning to play, some athletes who have undergone the surgery cannot perform as they did previously because a sense of knee instability remains and the muscle strength does not sufficiently recover. The causes of these unsatisfactory outcomes include the complication of meniscal injury[8], time from injury to reconstruction surgery, progression of osteoarthritis (OA), weakness of the quadriceps, joint laxity such as hyperextended knee, and anatomical characteristics such as excessive posterior tibial slope together with narrow intercondylar fossa[9].

The common causes of ACL reconstruction failure include new traumatic events (38%), technical failure (22%), and combined causes (19%)[10]. Anatomical ACL reconstruction can reduce the risk of post-traumatic OA[11]. Factors associated with postoperative outcome include drill hole position, method of fixation, mechanical strength of the tendon graft, drilling method, whether the ACL remnant is preserved, pediatric patients before epiphyseal closure and treatment of the meniscus[12].

Because ACL reconstruction enables athletes to return to sports and also people of working age (15–65 years old) to return to work[13], it can contribute to maintaining and activating industries in their communities. Although ACL reconstruction has offered great benefits, particularly to athletes and physical laborers, there is a great deal of room for improvement through technology development aimed at achieving more excellent outcomes and restoring performance to a level equal to or higher than before the injury.

In this paper, we outline current techniques for ACL reconstruction, describe their features and problems, and discuss expected future trends.

SURGICAL TECHNIQUES

Graft materials

Preparation: Hamstrings: The hamstring tendon is harvested by making a 3–4 cm skin incision 2 cm distal to the medial tibial articular surface. First, the sartorius tendon is divided along the length of the tendon. The underlying gracilis tendon is confirmed and pulled proximally. The semitendinosus tendon is confirmed distally. The distal branch of the semitendinosus tendon is dissected, bluntly detached with forceps and a gauze ball, and collected using a tendon stripper. If the semitendinosus tendon is short or thin, the gracilis tendon is also harvested.

Bone–patellar tendon–bone: The bone–patellar tendon–bone (BTB) graft is harvested by making a longitudinal skin incision of approximately 5 cm along the medial edge of the patellar tendon. An incision is made in the central 9–10 mm of the width of the patellar tendon with a scalpel. Trapezoidal bone fragments with a width of 8–10 mm and a length of 15 mm are collected from the patella and tibial tuberosity. In a BTB graft, when the length of the tibial tunnel is short and the patellar tendon is long, the bone fragment on the tibial side is exposed outside of the tibial bone tunnel. Thus, it is necessary to prepare a fixture such as a post screw.

Quadriceps: The surface layer of the quadriceps is the rectus femoris tendon. The middle layer consists of the tendons of the vastus medialis and vastus lateralis muscles. The deep layer is the vastus intermedius tendon. The width is narrowest approximately 5 cm proximal to the patellar attachment[14]. To harvest the quadriceps tendon, a scalpel is used to make a full-thickness incision 5–6 mm from the patellar attachment to the proximal end of harvested tendon. Next, an incision is extended up to the patellar attachment along the length of the tendon. The width of adherent portion is 8–10 mm. Next, a tendon with a thickness of approximately 10 mm is harvested. A Krackow suture is performed with two sets of No. 2 sutures. The length of the grafted tendon can be easily adjusted.

On the patellar side, a trapezoidal bone fragment with a length of 15 mm and a width of 8–10 mm is harvested. Even if the width of the quadriceps tendon is 5–6 mm, the thickness (approximately 10 mm) is sufficient in combination with the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius. The cross-sectional area of the quadriceps tendon is almost twice that of the BTB graft. The quadriceps tendon has higher load to failure and stiffness than the BTB graft[15]. The quadriceps tendons may be easier to use than the BTB graft in patients with anterior knee pain and pain during kneeling[16]. To fix the grafted ligament, an interference screw or a cortical button such as the CL-BTB is used as a patellar fragment on the femoral side. The thread is tied tightly to the cortical button on the tibial side.

Hamstring and BTB is commonly used as autografts[17]. Several studies reported no significant difference between these materials in postoperative clinical outcome; knee stability evaluated by KT-1000 (MED metric, San Diego, CA) test, Lachman test, and/or pivot shift test; International Knee Documentation Committee (IKDC) score; knee injury and osteoarthritis outcome (KOOS) score; limitation in range of motion; or the rate of return to sports[18-21]. However, there are some reported that the rate of graft rupture was slightly higher in patients who used hamstring autograft than in those who used BTB autograft[22-24] (Table 1).

Characteristics: Hamstrings: Among the hamstrings, the semitendinosus tendon and gracilis tendon are most commonly used for ACL reconstruction in patients, including amateur athletes[25]. If possible, it is preferable to harvest only the semitendinosus tendon, in order to prevent postoperative muscle weakness[26]. For single-bundle ACL reconstruction, the semitendinosus tendon is folded into four layers to obtain a diameter ≥ 8 mm. If sufficient length or diameter of autograft cannot be obtained, there is no choice but to use the gracilis tendon. A possible solution when performing ACL reconstruction using only the semitendinosus tendon autograft is to fill the socket-like drill tunnels with graft and use a technique with fewer bungee cord and windshield wiper effects. Harvesting the hamstring may result in reduced mobility of the knees at a high flexion position in some cases such as ballet dancer. An advantage of ACL reconstruction with hamstring autograft is that it makes it easy to perform double-bundle ACL reconstruction (Table 1).

BTB: ACL reconstruction with BTB autograft has commonly been used around the world because the patellar tendon provides high mechanical strength and interference screws provide strong fixation. However, because the autograft is harvested with bone, this technique causes postoperative tenderness of the anterior knee region where harvest was performed. This pain can persist for several years. Accordingly, the use of BTB autograft might be avoided for people in some Asian countries where it is

Table 1 Characteristics of various autograft materials

	Hamstrings	BTB	Quadriceps
Cross-sectional area	Good to excellent	Fair to good	Good to excellent
Mechanical strength	Good	Good to excellent	Excellent
Adjustment of graft length	Possible	Difficult	Easy
All-inside technology	Easy	Sometimes difficult	Easy
Preservation of remnant	Possible	Sometimes difficult	Sometimes difficult
Double bundle	Easy	Difficult	Possible
Graft fixation			
Femoral	Cortical button	Interference screw	Interference screw
		(metalic > bioabsorbable)	(metalic > bioabsorbable)
		Cortical button	Cortical button
Tibial	Cortical button	Interference screw	Cortical button
	Interference screw	(metallic ≥ bioabsorbable)	Interference screw
	(metalic < bioabsorbable)		
	Post fixation		
Complication	Nerve injury	Patellar fracture	Patellar fracture
	(infra-patellar branches of the saphenous nerve)		
	Decrease of Flexor muscle strength	Kneeling pain	
		Anterior knee pain	
		Decrease of extensor muscle strength	Decrease of extensor muscle strength
Indication			
Recommend	Amateur athlete	Amateur and professional athlete	Amateur and professional athlete
		(high-intensity sports)	(high-intensity sports)
			Revision surgery
Not recommend	Ballet dancer	Wrestler, Judo, Karate	

BTB: Bone–patellar tendon–bone.

common to sit on the Japanese sitting or kneeling and for athletes that requires often kneeling, such as wrestler judo or karate. Even in these countries, however, BTB autograft is often considered to be the first choice in male patients who do high-intensity sports because it can provide better postoperative stability relative to ACL reconstruction with hamstring autograft[21,27,28] (Table 1).

Quadriceps: Reports on the use of quadriceps tendon autograft with or without a bone block have increased since 2015, although the method had been used previously in clinical practice. Some studies reported that the clinical outcomes of ACL reconstruction with quadriceps tendon autograft were comparable or superior to those of reconstruction with BTB or hamstring autograft[28-31], whereas other studies reported that the rate of graft rupture was higher in ACL reconstruction with quadriceps tendon autograft than in reconstruction with BTB or hamstring autograft [32]. ACL reconstruction with quadriceps tendon autograft has several advantages: it causes less pain in the anterior knee region because there is a bone plug on one side only[29,33], less risk of injury to the infrasaphenous branch and the procedure requires only a small skin incision[34]. By contrast, ACL reconstruction with BTB autograft damages the tibial tuberosity. Although several studies reported ACL reconstruction with quadriceps tendon autograft, most were based on short-term follow-up. Hence, further studies based on long-term follow-up are needed to explore the possibility of reduced muscle strength for knee extension associated with the procedure (Table 1).

ACL reconstruction with BTB or quadriceps tendon autograft temporary decreases muscle strength for knee extension because it damages the knee extensor mechanism.

In addition, reduced quadriceps strength may be exacerbate knee OA. Therefore, sufficient training for these muscles is required after surgery.

Allograft: ACL reconstruction with allograft is an alternative technique because it does not damage the patient's own tissues. Therefore, it has been performed widely in the United States and Europe, and its outcomes are comparable to those of ACL reconstruction with autograft. However, after a study reported that the rate of graft rupture in patients who underwent ACL reconstruction with allograft was higher than that in those who received autograft[35,36], the use of allograft for primary ACL reconstruction has gradually decreased, although ACL reconstruction with fresh frozen and non-irradiated allograft is sometimes performed for revision ACL reconstruction[37,38] and multiligament reconstruction. The use of allograft is generally not recommended for primary ACL reconstruction in elite athletes.

Techniques for femoral tunnel drilling

The most common technical error in ACL reconstruction procedure is femoral tunnel malposition (63%), which causes poor clinical outcome due to residual instability or graft rupture[39].

Independent drilling technique is a method for drilling femoral and tibial tunnels separately (Table 2). There are two types of independent drilling: 1) the anteromedial (transportal) technique, in which a femoral tunnel is drilled from the inside to the outside; and 2) the outside-in technique, in which a femoral tunnel is drilled from the outside to the inside on a footprint identified with a dedicated drill guide (Table 1).

Anteromedial technique: The arthroscope is inserted from the anterolateral portal with the knee bent to 120–130 degrees. The drill guide pin is inserted from the antero-medial portal. The pin tip is placed in the center of the femoral footprint of the ACL. After drilling, it penetrates from the lateral cortex to the skin surface. First, a PL bundle bone tunnel is made, followed by an AM bundle bone tunnel in the same manner. If the knee flexion angle is 120 degrees or less, blowout of the posterolateral cortex would occur[40-42], making it impossible to fix the femoral side; this increases the risk of peroneal nerve palsy.

Outside-in technique: The arthroscope is inserted from the anteromedial portal with the knee bent to approximately 90 degrees. The femoral drill guide is inserted into the joint from the anterolateral portal and held firmly in place. Next, the guide pin is inserted so that it does not shift from the center of the femoral footprint of the ACL. The drill-guided trocar should be placed on the femur. A skin incision should be made in the lateral thigh to locate the lateral cortex.

With the anteromedial and outside-in approaches, after creating the femoral bone tunnel, a tibial drill guide is used to create a tibial bone tunnel from the anterior surface of the tibia based on the bone tunnel diameter. Both techniques are useful in that they enable surgeons to accurately create a femoral tunnel on the target footprint. Although both techniques allow for accurate femoral tunnel positioning, some studies have reported that the outside-in technique is more effective because it results in a more oblique tunnel and a longer femoral tunnel relative to the anteromedial technique[43-45]. Disadvantages of the anteromedial technique include that it is associated with the risk of short femoral tunnel, posterior-wall blowout, and iatrogenic damage to the cartilage of the medial femoral condyle by a more horizontal direction of the femoral tunnel in Three-dimensional (3D) plane[41]. However, the anteromedial technique can also produce a long femoral tunnel by using a flexible reamer, and the risk of peroneal nerve paralysis associated with this technique can be avoided using a specific procedure[46,47]. Disadvantages of the outside-in technique include the need for small incision in the femur[42]. At present, the anteromedial technique is most commonly used in the world[48,49].

Transtibial technique: This is a classical drilling method for ACL reconstruction, a tibial tunnel is initially created using a tibial drill guide. An arthroscope is inserted from the anterolateral portal. A tibial drill guide is inserted into the joint from the anteromedial portal. The tip of the guide is applied to the footprint of the tibia and then a guide pin is inserted through the tibial tunnel to create a femoral tunnel (Table 1). The position of the femoral tunnel in this technique depends on the orientation and position of the tibial tunnel. Therefore, this technique is called dependent drilling. Some studies reported that the anteromedial technique was associated with less femoral tunnel positioning errors and provided better stability and clinical outcomes than the transtibial technique[10,50,51], whereas other studies reported no difference between these techniques in clinical outcomes, patient satisfaction, or rate of revision reconstruction surgery in recreational athletes[52,53].

Table 2 Features of independent and dependent techniques

	Independent technique		**Dependent technique**		
	Anteromedial	Outside-in	TT	Modified TT	TT with modified devices
Femoral tunnel position	Anatomical	Anatomical	Somewhat unanatomical	Anatomical	Anatomical
Complexity of technique	Relatively simple	Somewhat complicated	Simple	Simple	Simple

TT: Transtibial.

The independent drilling techniques (anteromedial and outside-in) allow for the creation of femoral tunnels at more anatomical positions than the transtibial technique [54]. To decrease the rate of erroneous femoral tunnel positioning with the transtibial technique, several technologies assist in determining the center of the femoral tunnel, *e.g.*, the Wire-navigator® device (a guidewire navigation device; Smith & Nephew Japan Inc., Tokyo, Japan), which is composed of a Navi-tip consisting of tibial and femoral indicators[55] and a laser-beam guided drill guide[56]. These devices can indicate the center of femoral tunnel.

In the modified transtibial technique, the patient's leg is placed in a figure-of-4 position (the knee is in 90° flexion, varus and internal rotation of the tibia, and the hip is abducted) when the guide pin is inserted[57,58]. This technique is easy to perform for many surgeons who are accustomed to the transtibial technique[59]. Some studies reported that this technique resulted in better femoral tunnel positioning than the transtibial technique, as well as femoral positioning and clinical outcomes comparable to those of the independent techniques; in addition, the technique is easy to perform [58,60-62].

In our opinion, it is not ideal to perform the transtibial technique in the classical manner, relying on the surgeon's experience or gut feeling, because in some cases it results in poor femoral tunnel positioning. Therefore, if the transtibial technique is performed, assistive devices such as a dedicated drill guide should be used, and the patient's leg should be placed in a position suitable for this technique. To confirm the femoral tunnel position, some studies have recommended using arthroscopic views through the anteromedial portal as well as intraoperative fluoroscopic views[39].

There are knacks and pitfalls in any of the techniques mentioned above. Therefore, it is important for surgeons to master techniques that they are good at, taking their learning curve into account.

All-inside technique

The all-inside ACL reconstruction technique (Figure 1) is a relatively new, minimally invasive method in which both femoral and tibial tunnels are drilled from inside the joint[63-65]. It has recently become more common in clinical practice, and the number of its case studies has been increasing[66]. The all-inside technique may be a reasonable option. When drilling femoral and tibial tunnels using this technique, special care should be taken not to damage the trabecular bone structure adjacent to the graft and the sutures used to pull the graft. This technique can alleviate postoperative pain because it causes less damage to the tibial bone and the periosteum [67-69]. Moreover, it allows for creation of an autograft using only the semitendinosus tendon by the hamstrings tendons. All-inside ACL reconstruction with a semitendinosus tendon autograft has achieved good postoperative stability of the knee relative to ACL reconstruction with an autograft using both the semitendinosus tendon and the gracilis tendon[70] and ACL reconstruction with BTB[71].

For the all-inside technique, independent drilling with a retrograde drill is commonly performed, and devices that have been modified for this technique are available[68,72,73]. In our hospital, we assemble a dedicated guide pin and reamer in the joint, fix them, and drill the tunnels from inside the joint using the dependent technique[74]. We have achieved good postoperative outcomes in transtibial ACL reconstruction procedures, in which the center of the femoral footprint is irradiated with a laser beam to determine the tunnel position[75]. To date, we also have achieved good postoperative stability in patients who underwent transfemoral all-inside ACL reconstruction.

The advantages of the all-inside technique include less postoperative pain[68] and less bleeding, which may decrease the risk of postoperative infection. If this technique becomes less complicated, more surgeons may choose it (Table 3).

Table 3 Features of the conventional technique and all-inside technique

	Conventional technique	All-inside technique
Invasiveness in the tibial tunnel		
Bone damage	Moderate	Minor
Bleeding	Moderate	Minor
Invasiveness during autograft harvesting	Minor or moderate	Minor
Postoperative pain	Moderate	Minor
Complexity of surgery	Minor	Moderate

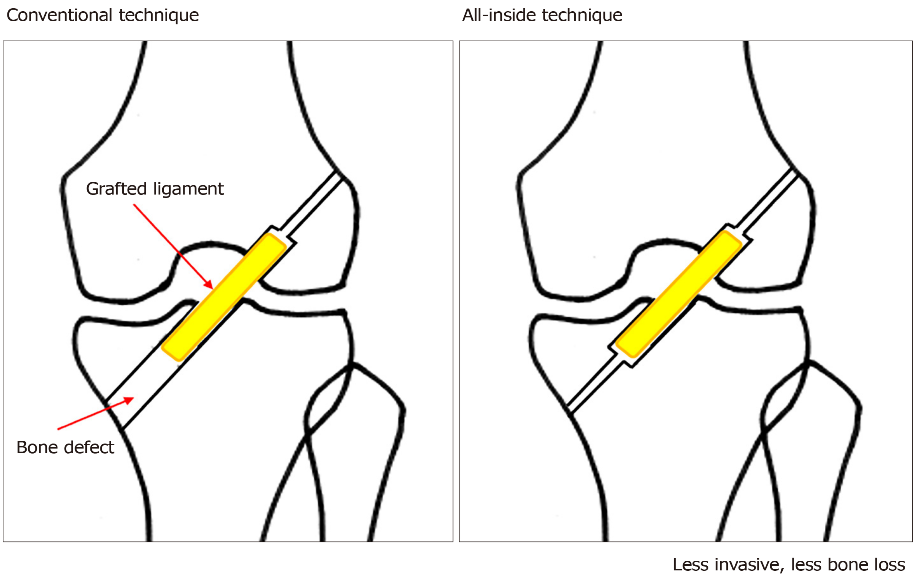

Figure 1 Schema of bone tunnel creation of anterior cruciate ligament reconstruction. Left: Conventional technique; Right: All-inside technique.

In most all-inside ACL reconstruction procedures in which both ends of an autograft are fixed with cortical buttons, only the semitendinosus tendon is used to create the autograft. In such cases, it is possible to create a large-diameter autograft and to obtain a better knee flexion strength in comparison with ACL reconstruction using both the semitendinosus tendon and gracilis tendon[76]. Several studies reported that all-inside ACL reconstruction using adjustable-length loop cortical button fixation resulted in less tibial tunnel widening than ACL reconstruction using bioabsorbable interference screw fixation[77,78], suggesting this approach may avoid two stage revision in revision ACL reconstruction surgery. However, there is no difference between these techniques in postoperative knee stability, clinical outcome, or rate of graft rupture[79]. It is expected that discussion of the benefits and reliability of the all-inside technique will become more active, as at present there have been few reports describing its long-term outcomes (≥ 5 years).

Double-bundle or single-bundle ACL reconstruction

Since the double-bundle ACL reconstruction technique was reported by Muneta *et al* [80] in 1999, it has been used around the world.

A double bundle consists of two routes: AM and PL bundles. Two bone tunnels are created for the femur and tibia, respectively. The graft material consists of hamstring autograft or allograft. In most cases, a hamstring autograft is used. The anteromedial approach is often used to create bone tunnels, but the transtibial or outside-in approach may be used.

An arthroscopic ruler can be used to measure the insertion site of the patient's native ACL. This measurement can help decide whether to perform double- or single-bundle reconstruction[81]. When a patient has femoral and tibial insertion sites that are larger than 14 mm, double-bundle reconstruction is indicated. When a patient has a notch width of less than 12 mm, double-bundle reconstruction often cannot be performed because the AM guide pin cannot be placed in the native femoral insertion site.

Comparing with single-bundle ACL reconstruction, double-bundle ACL reconstruction can better reproduce the natural anatomical structure of the ACL and provide better ACL function. In addition, several studies reported that double-bundle ACL reconstruction had a lower positive rate in the pivot shift test than that of one-bundle ACL reconstruction[82-84]. Moreover, double-bundle ACL reconstruction is more effective for improving rotatory instability. The rate of revision ACL reconstruction was lower in patients who received double-bundle ACL reconstruction in their primary surgery[85]. In addition, patients who received double-bundle ACL reconstruction exhibited less widening of the bone tunnel diameter, which leads to joint instability of the knee, than those who received single-bundle ACL reconstruction [86].

However, there was no difference between these techniques in the incidence of side-to-side difference evaluated by KT–1000 testing, Lysholm score, KOOS score, or in the rate of graft rupture[87,88]. Specifically, there was no difference in 5-year or longer outcomes between them.

Although the double-bundle ACL reconstruction technique is commonly used in Japan, the single-bundle ACL reconstruction technique is very common in other countries, including the United States. This may be because single route by BTB autograft is performed in many cases in those countries.

The advantages of single-bundle ACL reconstruction with hamstrings autograft include low costs of material fixation: because the autograft is fixed only at two positions, the number of devices required for fixation is half of that required for the double-bundle technique. In addition, surgical time is shorter because fewer bone tunnels need to be created. There is ongoing discussion regarding which technique is better. Therefore, further studies may be necessary to compare the progression of OA, the rate of graft rupture, and knee stability between single- and double-bundle techniques based on long-term follow-up.

ACL graft fixation techniques

Ten to sixteen percent of patients who undergo ACL reconstruction need revision ACL reconstruction due to new traumatic events or poor postoperative outcomes[89]. Therefore, the fixation technique for the primary ACL reconstruction should be selected to avoid challenging or highly-invasive procedures in possible revision ACL reconstruction surgery.

Currently available fixation techniques for ACL reconstruction include one method in which the ligament substance and bone parts are fixed with interference screws, and another method in which an ACL graft with a suture or artificial ligament is fixed with cortical buttons, post screws, or staples and so on.

A literature review study comparing suspensory fixation with interference screw fixation reported that suspensory fixation resulted in less side-to-side difference in KT-1000 measurements, whereas the interference screw exhibited a higher incidence of ligament rupture; however, there was no difference in IKDC scores between the two approaches[72,90].

Suspensory cortical button: The EndoButton is most commonly used for femoral fixation because it allows for easy and strong fixation and achieves favorable long-term outcomes[25,91]. The CL-EndoButton and CL-BTB EndoButton are available as fixed-loop devices. Recently, adjustable-loop devices have been increasingly used in clinical practice. Such devices are believed to be useful for filling gaps in bone tunnels. Some studies that performed comparisons of mechanical strength between fixed-loop and adjustable-loop devices reported that fixed-type loop devices have higher maximum tensile strength with less displacement[77,92-96], whereas other studies reported no difference between them[97-99]. In a clinical study, no difference in KT-1000 arthrometer measurements was observed between the two types of devices[100]. A modified suspension device with higher tensile strength and stiffness that was recently developed makes graft fixation easier under tension[101], and is expected to be used in clinical practice.

Interference screw: Interference screw fixation is most commonly used in ACL reconstruction with BTB because it provides strong fixation[102]. Although many interference screws are made of titanium, which has high biocompatibility, bioabsorbable interference screws are also used in clinical practice. It should be noted that, in some cases, titanium screws implanted into bones may be difficult to remove in revision ACL reconstruction. Interference screw fixation is commonly used for metallic one in femoral side, for absorbable one in tibial side.

Staple: Staples are commonly used to fix an artificial ligament to the bone when both ends of the graft (*i.e.*, the fixation parts inside the bone tunnels) are reinforced with an artificial ligament. Although they provide strong fixation, care should be taken to prevent bone damage that may occur if the cortex of the tibia is vulnerable.

Post-screw: The ACL graft is anchored to the tibia by inserting a post screw with a washer at the distal part of the tibial tunnel. This technique is easy to perform.

Cross-pin: Fixation of an ACL graft with a cross-pin on the femoral side is associated with lower rate of graft rupture[103]. This technique has been used mainly in Europe and the United States, but its frequency has been decreasing.

Double spike plate: The plate is fixed to the tibia by hammering its spikes into the bone under the index tension. Finally, the fixation is completed by inserting a screw [104].

Preservation of ACL remnant

There are two options for preserving the ACL remnant: (1) Selective augmentation of the anteromedial or posterolateral bundle that is partially damaged[105]; and (2) Double-bundle ACL reconstruction while preserving the ACL remnant[106,107].

One advantage of ACL remnant preservation is that mechanoreceptors preserved in ACL remnant and promote angiogenesis. In addition, this approach is associated with less anterior tibial translation and a lower rate of positive pivot-shift test. Despite these advantages, this technique may cause cyclops lesion. However, one study reported no difference in Lachman test, pivot shift test and IKDC score between ACL reconstruction techniques with or without remnant preservation[108]. In general, small scarred bundles of the anteromedial or posterolateral bundle are augmented in ACL reconstruction with remnant preservation. If preservation of the ACL remnant makes it difficult to create bone tunnels at appropriate positions, it is important to remove the remnant.

Anterolateral ligament reconstruction

Claes *et al*[109] named the ligament-like tissue on the lateral margin of the tibial plateau the anterolateral ligament (ALL). ALL reconstruction is an extra-articular procedure that has recently been performed in combination with standard ACL reconstruction[110]. This combination technique achieves favorable outcomes with a low rate of graft failure[111]. The anterolateral complex of the knee contributes to anterolateral rotatory stability as a secondary stabilizer to the ACL[112], although surgical reconstruction of the anterolateral complex may cause constraint of internal rotation of the tibia[113]. Combined ACL and ALL reconstruction are performed mainly in Europe, but its indication is limited to patients who have severe knee instability due to injury of ACL and other combined ligaments, or who have severe knee instability after ACL reconstruction because it is a highly invasive procedure.

A study on the addition of a lateral extra-articular tenodesis (LET) to ACL reconstruction with BTB graft reported no significant differences in long-term outcomes after ACL reconstruction with or without an LET, but LET may increase the risk of lateral compartment OA[114]. Another study reported that ACL reconstruction in combination with LET was associated with a higher risk of tunnel convergence[115].

Current graft options for ALL reconstruction include iliotibial band, gracilis tendon autograft or allograft, and semitendinosus tendon autograft or allograft; fixation angle varies from 0° to 90°[116]. Further prospective studies, such as a randomized control trial, are needed to compare clinical outcomes, indications and fixation techniques between ACL reconstruction with and without ALL reconstruction[116].

ACL repair

ACL repair with suture anchor for patients with avulsion ACL tears[117], as well as ACL repair combined with biologic healing augmentation for patients with incomplete tears[118], achieves successful outcomes.

An ACL repair technique with additional internal bracing was introduced in a recent study[119-122]. A study of this technique based on a short-term follow-up with small sample size reported that its outcomes were comparable to those of ACL reconstruction[123]. ACL repair may be a good treatment option for partial proximal ACL tears and pediatric ACL tears[124,125]. Although a systematic review of contemporary studies revealed no differences between ACL repair and reconstruction with respect to knee stability and the rate of graft rupture, further studies are needed because these studies were based on short-term follow-up with small sample size[123].

Complication

Infection and its prevention: The incidence of knee joint infection after ACL reconstruction is low because it is performed arthroscopically with saline irrigation [126]. However, infection has been reported to occur in 0.14% to 2.6 % of patients who undergo ACL reconstruction[7,127,128]. The most common pathogen of infection after ACL reconstruction is *Staphylococcus aureus*. Acute infection can be caused by pathogen contamination of the tibial tunnel or the skin incisions made for arthroscopy [126]. Pre-soaking hamstring autografts in gentamicin reduce intra-articular infection rates[129]. Bleeding and subcutaneous hematoma of these sites after surgery can also be a cause of infection. Therefore, it is important to decrease the amount of bleeding by icing and to treat wounds carefully. On the other hand, chronic infection can be caused by screws and tendon suture materials[126]. Special care should be taken for patients with atopic dermatitis, as these patients have a higher infection risk.

Deep vein thrombosis: The incidence of deep vein thrombosis after ACL reconstruction ranges from 0.3%[130] to 0.4%[131]. The incidence of pulmonary embolism is 0.18%[130] to 0.046%[130]. The only significant risk factor is age. Therefore, thromboprophylaxis should be considered in older patients.

Hemarthrosis: Hemarthrosis after ACL reconstruction can delay rehabilitation. The use of intravenous tranexamic acid in ACL reconstruction results in reduced joint drain output and hemarthrosis as well as less pain and greater range of motion during the early postoperative period[132]. Tranexamic acid does not increase the risk of deep vein thrombosis after surgery[133].

Joint stiffness: The incidence of joint stiffness after ACL reconstruction is overall 3% [134] to 8.8%[135]. There was no significant difference between BTB graft and hamstring tendon with respect to the frequency[135] and the interval between trauma to surgery[134].

Cyclops syndrome after ACL reconstruction is due to a fibrous nodule in the anterior part of the intercondylar notch. It restricts the full extension of the knee[136]. The incidence of symptomatic cyclops syndrome ranges from 1.9% to 10.9%[136].

Arthrofibrosis is a rare but potentially devastating complication after ACL reconstruction[7]. Approximately 2% of patients have postoperative stiffness that requires intervention[137]. However, arthrofibrosis remains poorly defined and there are no clear treatment guidelines[138].

Nerve injury: Tendon harvesting for ACL reconstruction often injures sensory branches of the saphenous nerve[139]. Injuries to the sartorial branch of the saphenous nerve associated with medial incisions for hamstring tendon harvesting are more common than injuries to the infrapatellar branch associated with midline incisions for patellar tendon harvesting[139]. Numbness of the skin surface supplied by the infrapatellar branches of the saphenous nerve after ACL reconstruction are less common with the quadriceps tendon compared with the hamstring tendon[140]. Regarding hamstring tendon harvesting for ACL reconstruction, vertical incisions increase the risk of iatrogenic injury to the IPBNS compared with oblique incisions[141-144].

Patellar fracture: The incidence of patellar fracture during BTB harvesting ranges from 0.3%[135] to 1.3%[145]. It is a rare but serious complication[146]. To eliminate the risk of perioperative patellar fracture, the bone-tendon-autograft technique, which does not harvest the inferior patellar bone, might be an alternative graft option[147].

The incidence of intraoperative patellar fracture after harvest of a quadriceps tendon autograft is reported to be 3.5%. It is necessary to use care when harvesting the bone block from a central position[148] and to limit the depth of bone harvesting to less than 50% of the depth of the patella with a shorter bone plug length. Longitudinal cuts can be angled centrally to produce a trapezoidal bone block with shallower bone removal[148].

Our methods for ACL reconstruction

We usually use only the semitendinosus tendon for primary ACL reconstruction. We produce the bone tunnel with the all-inside method using a single quadruped semitendinosus graft. We fix the grafted ligament with a cortical suspension button on both sides. In the all-inside method, the knee is flexed to approximately 90 degrees, the lower leg is internally rotated, and varus stress is applied to the knee using the dependent method.

We developed a tibial drill guide with a laser beam that can identify the optimal location for the femoral tunnel during creation of tibial tunnel in a modified transtibial method. We used it in a clinical application during ACL reconstruction.

The new drill guide system: The structure of the tibial drill guide with a laser beam is shown in Figure 2. This laser beam-guided technique with a special tibial drill guide produces both tibial and femoral tunnels. The laser pointer was visible light semiconductor laser, maximum output energy of 1mW. The guide contains a metal tube for passage of laser beam (Figure 3), which can be filled with saline for irrigation. The reflected beam indicates appropriate position on the extension of the pin (Figure 4). Figure 5 shows an arthroscopic photography with the laser beam.

Transtibial guide pin placement and tunnel placement: The special drill guide is inserted through the anteromedial portal, and placed at the anatomical tibial foot print. A laser beam is reflected by reflecting plate of tip of the guide. The laser pointer illuminates the tunnel which is where femoral bundle should be made appropriately (Figure 4). A transtibial guide pin of 2.4 mm in diameter is inserted into the intra-articular portion of proximal tibia. The diameter of tibial tunnel is similar to that of grafted tendon. The guide pin is set at appropriate location of femoral tunnel. Method of making femoral tunnel and graft fixation was performed according to our previously described[56,75]. Our method is a useful way to select an appropriate anatomical site for the bone tunnels accurately and obtain excellent clinical results with ACL reconstruction.

Recently, we have produced and used a drill guide for the all-inside transfemoral method. The grafted ligaments are fixed with a CL-BTB endobutton on the femoral side and a cortical button on the tibial side with knee flexion of approximately 20 degrees. We often use a BTB graft to obtain strong fixation for young men who are active athletes needing to withstand strong collisions, such as in rugby and football. However, the quadriceps tendon is also useful. Residual ligaments are often preserved if they are thin but relatively tense. At this time, double-bundle reconstruction with residual ligaments is not performed because it is difficult to make two bone tunnels at appropriate positions. We reconstruct the AM or PL bundle based on preoperative MRI evaluation and intraoperative arthroscopic findings. ACL reinforcement is often performed to reconstruct the PL bundle, which can lead to definite symptoms of rotatory instability.

In revision reconstructive surgery, we use the ipsilateral semitendinosus tendon, BTB graft, or quadriceps tendon with a patellar fragment, unless the tendon has already been used. Quadriceps tendon with a patellar fragment has excellent mechanical strength. Reconstruction can be performed with the all-inside method, which reduces trabecular damage in the bone tunnel. Thus, we plan to increase its use in the future. At this time, the grafted ligament is fixed with a patellar fragment on the femoral side using an interference screw. On the tibial side, the grafted ligament is fixed with a cortical button, which is sutured using the Krackow method with two sets of no. 2 sutures.

REVISION ACL RECONSTRUCTION

Some patients may need to receive revision ACL reconstruction due to graft rupture or residual knee instability.

One-stage or two-stage revision ACL reconstruction

When an ACL graft cannot be fixed at an appropriate position because the bone is severely damaged, bone tunnel grafting with an Iliac bone autograft is performed in two-stage revision ACL reconstruction[149]. In most cases, however, one-stage revision ACL reconstruction is selected because the two-stage procedure requires time for healing after bone grafting.

Techniques for revision ACL reconstruction

Prior to revision ACL reconstruction, computed tomography scanning is performed to three-dimensionally assess the positions and sizes of bone tunnels created in the primary surgery and to determine the positions of bone tunnels for revision ACL reconstruction. During the assessment, it is important to confirm the type of fixture used in the primary surgery. It should be noted that, if titanium interference screws were used in the primary surgery, it may become more difficult to remove them over

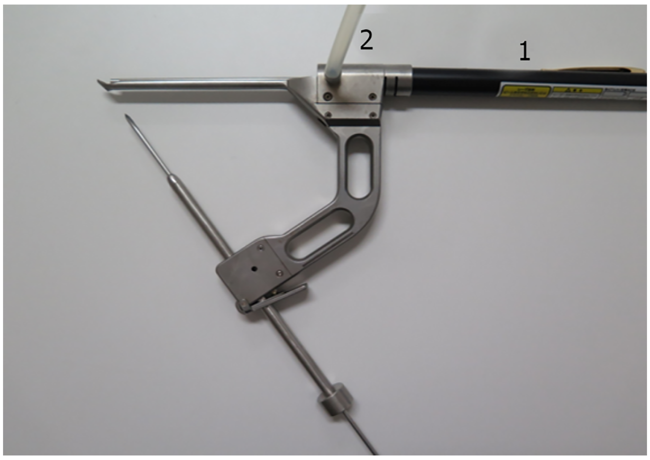

Figure 2 Structure of the tibial drill guide equipment with a laser beam. The laser beam pointer (1); The irrigation tube (2).

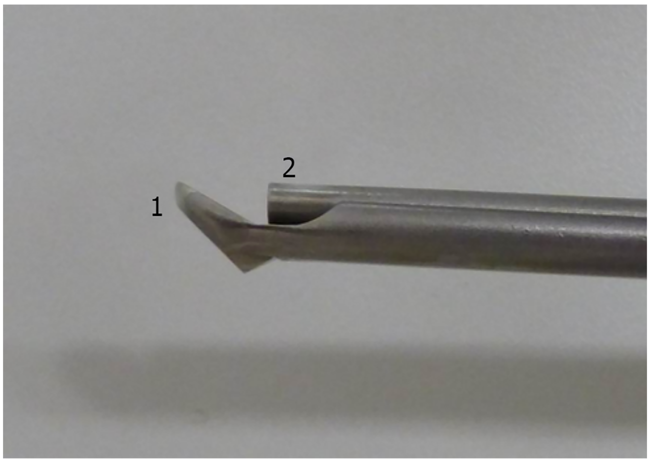

Figure 3 The tip of the tibial drill guide equipment. Reflecting plate (1); Straight metal tube for passage of laser beam (2).

Figure 4 Reflected beam identifying the proper position on the extension of the pin.

time: due to the high biocompatibility of titanium, the screws become surrounded by bone on both femoral and tibial sides. Therefore, appropriate screw drivers should be prepared to remove them. Besides BTB and hamstring grafts, a quadriceps tendon graft is often used in revision ACL reconstruction because it has advantages in terms of strength and diameter[150].

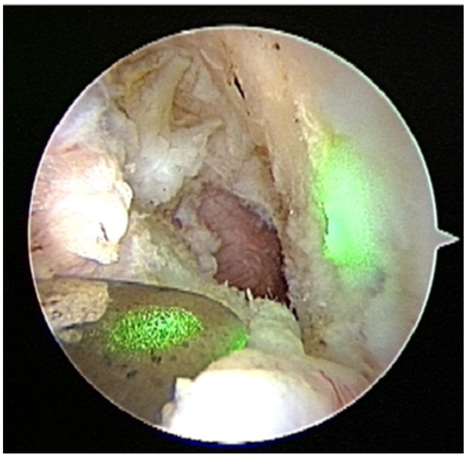

Figure 5 Arthroscopic photography with laser beam. Reflected beam illuminating the foot print of the femoral tunnel.

Postoperative outcomes of revision ACL reconstruction

Several studies reported that revision ACL reconstruction is inferior to primary reconstruction in postoperative outcomes and the rate of returning to sport[151,152]. However, the data regarding long-term clinical outcomes from large-scale cohort studies are limited; accordingly, further studies are needed[150].

TREATMENT FOR ACL INJURY WITH KNEE OA

ACL insufficiency persisting after ACL injury often accelerates age-related OA change, worsens wear of cartilages of the medial knee joint, and results in varus deformity. In this case, ACL reconstruction in combination with high tibial osteotomy (HTO) is indicated for individuals younger than 70 years old who want to engage in a high level of physical activity such as sports or heavy physical labor and have less OA change in the patellofemoral joint[153,154]. Slope-reducing tibial osteotomy with this combination procedure can further improve knee stability in patients with varus deformity and excessive posterior tibial slope[155,156]. There are surgical techniques for HTO include opening-wedge[157], closed-wedge[158], and dome-shaped[159,160] osteotomy. HTO should be performed with one-stage ACL reconstruction simultaneously, postoperative rehabilitation after HTO combined with ACL reconstruction can be performed in the same manner as rehabilitation after HTO alone. Long-term outcome regarding one-stage HTO and ACL reconstruction suggested that it is an effective and safe procedure[161]. A systematic review of studies on one-stage HTO and ACL reconstruction reported that the percentages of patients who received opening-wedge and closed-wedge HTO were 57.4% and 42.6%, respectively, and the percentages of patients who received hamstring and BTB autograft for ACL reconstruction were 85.6% and 12.8%, respectively[162]. Although currently available data indicates high patient satisfaction and high rate of returning sport after combined with HTO and ACL reconstruction[163], further studies are needed to compare clinical outcomes between combined with HTO and ACL reconstruction and HTO alone.

FUTURE ACL RECONSTRUCTION

Biological augmentation of ACL repair and reconstruction

In most studies, ACL repair resulted in failure or unfavorable results. Recently, however, experimental and clinical studies on biological augmentation of mesenchymal stem cells, platelet-rich plasma (PRP), or other biologic agents with scaffold are being conducted to assess the effects of such biotherapies on ACL repair and reconstruction[164,165].

The four main components of tissue engineering such as cells, growth factors, scaffolds, and mechanical stimuli, are combined using various methods of bioaugmentation. They have been increasingly explored to improve outcomes after surgical treatment of ACL injury[164,166-169].

Scaffolds: Stem cell-based tissue regeneration combined with scaffolds represent a novel treatment for torn ligaments[170-172]. 3D scaffolds seeded with mesenchymal stem cells yielded excellent results in osteointegration enhancement between the tendon and bone tunnel in ACL reconstruction with a rabbit model[173]. PRP combined with a gelatin sponge to prolong PRP bioactivity promotes mesenchymal stem cell proliferation *in vitro*[174].

Cell sources: The main cell sources are mesenchymal stem cells and ACL fibroblasts [175]. Mesenchymal stem cells have higher proliferation and collagen production rates than ligament fibroblasts[176]. ACL-derived human-induced pluripotent stem cells might be a promising cell source for ligaments and related tissue engineering applications[177].

Growth factors: PRP is obtained by plasma separation. PRP contains platelets, blood proteins such as fibrin, and a mixture of growth factors such as platelet derived growth factor, insulin-like growth factor, vascular endothelial growth factor, and transforming growth factor-beta, which are involved in general healing processes.

PRP has been used to treat knee OA and to promote ligament healing. Recently, it has been used experimentally in ACL reconstruction to promote graft maturation and osteointegration[178]. However, no clinical efficacy data have been reported yet[179, 180].

Mechanical stimulation: Mechanical stimuli and dynamic loading are necessary for ligaments to enhance matrix synthesis and maintain their strength[181]. Electrospinning has been effective for cell proliferation and extracellular matrix production of scaffolds for ligament tissue engineering[182]. However, whether any mechanical stimulation is required to implant tissue-engineered ACL constructs is controversial [175].

In recent studies, bioenhanced ACL repair had similar results as ACL reconstruction. These biotherapies are expected to reduce postsurgical OA and to be improved in the future.

Computer-aided surgery

In other clinical departments, robotic surgery with the da Vinci™ Surgical System (Intuitive Surgical, Sunnyvale, CA, United States) has become more widespread, mainly in large-scale hospitals. In orthopedic surgery, computer-assisted navigation has come to be used for spine surgery[183-186], total hip arthroplasty, and total knee arthroplasty[187,188].

There are four main types of applications for navigation systems in ACL reconstruction[189,190]: (1) Technical assistance of tunnel placement for tibial or femoral tunnel drilling; (2) Kinematic evaluation to analyze the biomechanical behavior of the ACL and surrounding structures during reconstructive surgery[191]; (3) Comparison of the effectiveness of different surgical techniques for making laxity measurements[192]; and (4) Navigation to improve clinical outcomes and cost-effectiveness of ACL reconstruction.

3D fluoroscopy-based navigation system: It is essential to perform preoperative planning using 3D computed tomography (CT) images before operation. A reference frame is rigidly attached to the femur with two half-pins at the beginning of surgery. An intraoperative 3D image of the distal femur is obtained with the C-arm of the image intensifier, which is equipped with a wireless tracker. The image is reconstructed into a 3D image on the computer screen. A navigation computer helps the surgeon visualize the entire area for bone tunnel creation. However, this system requires fixation with two half-pins in the lateral femur, which necessitates an additional skin incision and more drill holes[193,194].

CT-based navigation without intraoperative fluoroscopy: This system uses a preoperatively generated 3D model from CT images or intraoperative 3D bone morphing with an optical tracking system. The optical tracking system captures reference markers that are rigidly attached to the patient and surgical tools. After fixing the tracking markers, approximately 20 Landmark points are collected on the surface of the bone with probes[195-197].

Anatomical reconstruction using the anteromedial technique is associated with more risks including: (1) A short femoral tunnel; (2) Posterior wall blowout; and (3) Iatrogenic damage to the cartilage of the medial femoral condyle due to the more horizontal direction of the femoral tunnel in the 3D plane[41]. Navigation systems with enhanced registration accuracy can reduce surgical failures such as short femoral tunnels and posterior wall breakage of the distal femur[195,198].

Image free navigation system: This method does not require preoperative CT or intraoperative fluoroscopy. The transmitters for the femur and tibia are fixed with pins to register intra- and extra-articular landmarks intraoperatively. Next, the transmitter is attached to the tibial drill guide to determine the location of the tibial bone tunnel. The same maneuver is used for the femoral bone tunnel[199].

There is considerable variability in intra-articular landmark identification with image- free navigation. There is a potential risk of miscalculating tunnel positions[200].

Guided drilling of the tunnel leads to errors as small as 2.5 mm in the footprint and in the orientation of the intra-operative video for guiding the drilling of the tunnel with a set of contours which is reconstructed by touching the bone surface with an instrumented tool[201].

There are some studies on the use of computer-assisted navigation for bone tunnel positioning and evaluating joint instability in ACL reconstruction[202-204]. Clinical, radiological, and functional comparisons between computer-assisted and conventional ACL reconstruction have found increased accuracy in femoral tunnel placement with the use of navigation systems compared with traditional techniques alone[196,204-207]. Some studies reported that computer-assisted navigation improved the accuracy of tunnel positioning[208-210]. For inexperienced surgeons, navigation systems could be useful in ACL surgery to avoid malpositioning of bone tunnels[211,212]. However, another study showed that experienced surgeons could achieve more accurate tunnel positioning than computer-assisted positioning[211]. Consequently, computer-assisted navigation has not become common in clinical practice.

Although currently available navigation systems can enable more accurate femoral tunnel positioning and assist less experienced surgeons[201], they are not cost-efficient and require extra time for registration of operative positioning data[190,213]. Moreover, there is no difference in clinical outcomes between ACL reconstruction with and without computer-assisted navigation[214]. Therefore, a completely new system with high efficacy needs to be developed.

3D fluoroscopy-based navigation systems might be useful for confirming the native ACL footprint in remnant-preserving ACL reconstruction[215,216]. Several studies have described the use of navigation-assisted surgery to increase the possibility of achieving adequate tunnel position in revision ACL reconstruction[194,217].

Kinematic assessment of knee laxity among different ACL surgical procedures have been evaluated[218,219].

With the advancement of robotic surgery, remote surgical assistance will be available. At present, most ACL reconstructions are performed in urban hospitals by arthroscopic surgery specialists. It is not recommended that ACL reconstruction would be performed by a surgical team with no training in the procedure. However, if remote surgery assistance becomes available, and ACL reconstruction can be performed in rural areas where advanced medical care is unavailable, it will be helpful for residents in these areas. The da Vinci™ Surgical System has already been used for remote surgery assistance in some hospitals. In laparoscopic surgery assisted by the da Vinci™ Surgical System, the robot arms in a local hospital are remotely controlled by an advising surgeon in an operating room of an advanced medical facility. Such remote assistance enhances the skills of surgeons in local hospitals. In the future, robot-assisted ACL reconstruction surgery could also be achieved by remote instruction or remote control of robot by an arthroscopic surgery specialist. We hope that these technologies make advanced ACL surgery available to people living in countries and regions where advanced ACL treatment is unavailable.

CONCLUSION

There is no question that ACL reconstruction is necessary in order for patients with ACL injury to maintain a high level of activities, including sports, and that the number of patients receiving ACL reconstruction will increase around the world. However, ACL reconstruction has not provided satisfactory results in terms of the rate of returning to sports and prevention of OA progression. To enable many more orthopedic surgeons to achieve excellent ACL reconstruction outcomes with less invasive surgery, further studies aimed at improving surgical techniques are warranted. Further development of robotic surgery technologies for ACL reconstruction is also required.

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REVIEW

Weight regain after bariatric surgery: Promoters and potential predictors

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Abstract

Obesity is globally viewed as chronic relapsing disease. Bariatric surgery offers the most efficient and durable weight loss approach. However, weight regain after surgery is a distressing issue as obesity can revert. Surgical procedures were originally designed to reduce food intake and catalyze weight loss, provided that its role is marginalized in long-term weight maintenance. Consequently, it is essential to establish a scientifically standardized applicable definitions for weight regain, which necessitates enhanced comprehension of the clinical situation, as well as have realistic expectations concerning weight loss. Moreover, several factors are proposed to influence weight regain as psychological, behavioral factors, hormonal, metabolic, anatomical lapses, as well as genetic predisposition. Recently, there is a growing evidence of utilization of scoring system to anticipate excess body weight loss, along with characterizing certain biomarkers that identify subjects at risk of suboptimal weight loss after surgery. Furthermore, personalized counseling is warranted to help select bariatric procedure, reinforce self-monitoring skills, motivate patient, encourage mindful eating practices, to avoid recidivism.

Key Words: Weight regain; Bariatric surgery; Hormones; Diet; Exercise; Genetic factors

Core Tip: Obesity constitutes an enormous health struggle worldwide. Weight regain after bariatric surgery is a distressing issue that requires extensive study; various influencing factors as well as predicting biomarkers must be considered carefully before making decision for surgery, selecting bariatric procedure as well as close long term monitoring and support are essential.

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INTRODUCTION

Morbid obesity is the consequence of cumulative imbalances between energy intake and energy expenditure[1]. It is a serious chronic disease causing various comorbidities reducing affected persons' well-being and lifespan. Bariatric surgery is an option in morbidly obese subjects when lifestyle and non-surgical strategies evidenced incompetent. It produces superior reduction in body weight along with relief of associated comorbidities compared to nonsurgical interventions[2]. There are several reputable techniques adopted in management of morbid obesity worldwide. However, Laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) are two most common weight loss procedures due to their significant weight reduction and durability[3,4].

Following bariatric surgery, body contouring occurs when operated subject finally achieves the required body mass index (BMI) in a comprehensive and stable basis, exhibiting proper nutritional, psychological and clinical aspects[5]. Since during weight loss, those subjects may encounter nutritional depletion along with metabolic adaptation, which compromises healing demands and the whole response to surgical stress[6,7]. Consequently, expected weight loss after successful surgical procedure progresses through several anticipated phases[3] (Table 1). However, stability phase outcome is frequently humbled in considerable number of patients, with regain of 5-10 kg, after weight stabilization which is expected and considered normal[4]. Though, in long-term surveillance, there is growing perception concerning the possibility of weight regain after bariatric surgery[6]. Kraschnewski *et al*[8] stated that less than 20% of operated subjects who achieved expected weight loss through various surgical procedures within the first year, experienced variable extent of weight regain within five years.

IDENTIFICATION OF POSTOPERATIVE WEIGHT REGAIN

In order to determine weight regain, it is essential to comprehend the definition of weight stability. Considering that it is expected to observe minor fluctuations in body weight. Rubin defined weight stability as less than 2.5 kg variation in body weight per month over the preceding three months[9]. Given that this issue is subjective; Various literatures proposed a postoperative period of 12-18 mo till body weight becomes stable, with no more fluctuations through the succeeding 4-6 mo[10-12]. Accordingly, definition for weight regain requires careful description by determining patient characteristics, such as baseline BMI, age, gender, surgical procedure, general health perceptions, preoperative comorbidities[13].

Voorwinde *et al*[14] introduced six definitions for weight regain after bariatric surgery based on reports of various researches: (1) An increase of more than 10 kg from body weight denoting weight regain after achieving desired weight stability; (2) An increase of more than 25% excess weight loss (% EWL) after achieving weight stability phase; (3) An increase in BMI of 5 kg/m^2 after attaining steady BMI; (4) Weight regain to a BMI more than 35 kg/m^2 from baseline after long standing follow up *e.g.*, five years; (5) Any weight regain; and (6) An increase more than 15% of total body weight from baseline after long period follow up *e.g.*, five years[14]. This is determined by using following equation (total body weight at end of follow up period – total body weight at baseline/ total body weight at baseline × 100 > 15[13,15].

Percentage of EWL refers to reduction in body weight after bariatric surgery. In brief, a subject whose ideal body weight ought to be 70 kg but weighs 130 kg before bariatric procedure, implies 60 kg excess body weight. Appropriately, an optimum weight loss response is generally termed as 50% EWL[10,16]. Then long term postoperative expected weight loss is approximately two-thirds (2/3) of initial body weight (60 kg excess weight) or 40 kg[17]. The ideal weight is customarily determined on the basis of body mass index of 25 kg/m^2[13]. This is obtained from a formula where the square of subject's height in meters is multiplied by 25. For instance, if

Table 1 Phases of weight changes after bariatric surgery

Phase name	Phase description
Weight loss Phase	Initial prompt weight loss period during which convalescent patient could lose up to 25 kg in the first month, this period persists for up to six months[3]
Pre-stability Phase	Afterwards, weight loss slacks off for approximately one year[3]
Stability Phase	Ultimately, through the subsequent two years usually convalescent patients attain lowermost body weight, (having lost about 50% of the excess body weight) is maintained in the majority (70%-80%) of patients, irrespective of surgical procedure performed[2]

subject's height is 1.8 m: (1.8 × 1.8) × 25 then ideal body weight is 81 kg[13].

In pursuit for clinically applicable outcome indicators, some authors referred to percentage of total weight loss (%TWL) as the most accurate metric for calculating weight loss post-operative[10,12]. They claimed that %TWL is minimally affected by perplexing preoperative variables as initial BMI, age, comorbidities particularly diabetes. Therefore, %TWL is simple, easy to estimate and understand[12,18]. It is often utilized in appraising behavioral and pharmacotherapeutic literature[18].

%TWL is determine by formula: (Pre-operative body weight – Current body weight) / (Pre-operative body weight) × 100[12].

Some authors recommend that %TWL applied routinely to quantify weight loss and suggest that ≥ 20%TWL within 12 mo become the established benchmark to identify good responders to weight loss surgery along with reporting of remission or improvement of obesity comorbidities. As well as to track long-term weight regain after bariatric surgery[18,19]. However, Corcelles *et al*[20] concluded that use of single variable such as %TWL to delineate weight-loss outcomes can generate deceptive evaluation of patients results. Consequently, they recommended use of more than one definition for weight loss including change in BMI or BMI loss percent EWL, percent %TWL, percent excess BMI loss, and percent total BMI loss[20].

Weight changes in two most common bariatric procedures: LRYGB vs LSG

In terms of short-term outcome; RYGB yields 60%- 80% of excess body weight loss (EBWL) within the first year. It is generally recommended for morbid obesity with BMI over 40[18,19]. On the other hand, LSG yields weight loss at a slower, steadier rate, about 60% of excess body weight is lost within first 18 mo[21,22]. However, several studies revealed that both procedures are equally effective measures for short-term obesity management (< 36 mo) in super obese subjects[23,24].

Pertaining to long-term outcomes; five years postoperative follow up significant weight regain is sporadic for patients undergoing RYGB 2.5%, whereas patients undergoing LSG 14.6%[11]. This conclusion was supported by other studies[25,26]. It is worth mentioning that bariatric surgery was originally intended to downsize the stomach in an attempt to reduce food intake and prompt weight loss, but research studies approved that it has a minimal role in long-term weight loss maintenance[15,16,27].

DETERMINANTS OF WEIGHT REGAIN

The etiology of weight regain tends to be multifactorial including behavioral and dietary habits, mental health, anatomical changes, hormonal variations and genetic aspects[27,28]. Certainly, it results from a combination of components, which vary among individuals' overtime[29]. Moreover, anticipation of weight regain should be mandatory in consultation with all parties; patient, surgeon and nutritionist prior to surgery, as it may influence patient's ability to avoid weight regain[28]. Madan *et al*[30] have observed that only 10% of patients could recall being enlightened about the possibility of weight regain after surgery.

Dietary habits and behavioral practices

Negative eating habits and lack of dietary modifications are risks to long-term postoperative failure. Therefore, to obtain maximum benefit from surgery, patients should be encouraged to adhere to appropriate dietary habits[31]. Since, weight regain commonly occur as result of poor assortment of healthy diets rather than excessive intake[29]. Sawamoto *et al*[32] reported that persistence of poor preoperative eating behavior after surgery was associated with 68.6% failure rate. Also, Felsenreich *et al* [33] found that unhealthy eating habit correlated with rate of 59% weight regain within 10 years after surgery. Nikiforova *et al*[34] obtained similar results, they proposed the explanation for weight regain include; sleeve or pouch dilation according to procedure performed, enhanced ghrelin levels, lifestyle behaviors and lack of follow-up support. Additionally, Mitchell *et al*[35] found a higher incidence of weight regain among subjects who consumed limited number of meals, less than 5 small frequent meals, and often skipped breakfast. Owing to a false belief that decrease in number of meals aids supplementary weight loss, whereas actually ingestion of numerous small meals per day augments diet-induced thermogenesis and stimulates smaller insulin secretion[32].

Healthy dietary deeds acknowledged among weight loss maintainers[36]: (1) Commitment to daily intake of breakfast as it assists stabilization of blood glucose level[31]; (2) Consumption of ample amounts of water, as optimal hydration prevent oxidative stress, while losing more than 2% of body water causes altered body temperature control, increased both physical and mental fatigue[36]; (3) Greater protein intake about 1.0-1.5 g/kg of ideal body weight per day, restriction of sugar less than 5 gm per serving and less than 30% of daily calories fat[30,37]; and (4) Ingestion of nutrients with low glycemic index and high dietary fibers contents such as fruits and vegetables prolong intestinal absorption[31]. Accordingly, Nutritional follow-up monitoring is consistently regarded as a vital element of medical management after bariatric surgery [38].

Mental health and psychiatric disorders

In this respect adverse eating behaviors could be a crucial factor; including emotional binge eating described as episodes of overeating even when not hungry, on exposure to emotional stimuli or stress to extent of causing gastrointestinal discomfort[31]. Similarly, Grazing is repetitive unplanned eating of minor quantities of food with loss of control over this feeding, associated with some psychological disturbance[39]. Also, distracted passive eating implies hyperphagia in presence of an element disturbing one’s attention from the quantity of food ingested as chatting with a friend or watching television[27,40]. Moreover, some individuals may display cravings for fats and sweets, described as addictive personality or could be regarded as cortisol-mediated response to stress[41]. Sugar craving phenomenon may possibly be induced by central metabolic actions, as serotonin or dopamine imbalance, altered leptin levels [41]. Cognitive behavioral consideration proves more effective in curing maladaptive eating disorders than sole nutritional counselling without managing psychological part[42,43]. Authentically, psychological conditions as grazing could lead to weight regain postoperatively, regardless of surgery type in about 16%-39% of patients postoperatively[44-46]. This considerably high incidence necessitates accurate assessment, close monitoring and attention to guidelines for nutritional management postoperatively recommending eating slowly, chewing food thoroughly, and increasing the frequency of meals[42].

Physical activity and lifestyle

Physical inactivity is considered a valuable component criticized of having a role in weight regain along with as sleep deprivation (sleeping less than the recommended amount) and television watching more than two hours daily, all may be associated with reduced sensitivity to the internal satiety signals[36]. Similarly, Petit *et al* deduced that sleep deprivation augments mood changes, upsets glucose metabolism and appetite regulation[47]. They suggested that sleep replenishes glucose stores in neurons while the awake cycle depicts recurrent glycogen breakdown[47].

Corresponding to American College of Sports Medicine proposals for weight loss and prevention of weight regain for adults; entailed performance of 150 min per week of moderate or vigorous physical activity [moderate < 3-6 metabolic equivalents (METs), vigorous > 6 METs][48]. In view that experts assessed exercise performance in MET. Where one MET is expressed as the amount of energy spent to rest quietly, for average adult one calorie per every 2.2 pounds of body weight per hour[49]. This signifies that moderate activity is enough to burn 3 to 6 times as much energy per minute than lying quietly[50]. American Society for Metabolic and Bariatric Surgery encourages the increase in physical activity to a minimum of 30 min per day[48]. Notably, within the first year postoperative, physical activity contributes to enhanced oxygen consumption with prompt adaptability in heart rate and improved lipid profile[51]. While, Freire *et al*[52] depicted that it has a negligible effect on short-term weight loss, but assists long term weight loss maintenance. Some studies reported that subjects engaged in moderate to vigorous physical activity achieved a greater % EBWL compared to others less physically active 2-5 years postoperative[53-55].

Anatomical modifications

RYGB bears a long-term failure rate of 20%-35%, particularly in super-obese population (BMI > 50 kg/m²) due to gastro-gastric fistula or disrupted staple line[56]. Gastro-gastric fistula is a communication between pouch and stomach remnant, which permits food to cross duodenum reducing restrictive and malabsorptive potentials of RYGB, but is alleviated by surgical revision as biliopancreatic diversion or duodenal switch[57]. Even though wide gastrojejunostomy or pouch dilatation could be anticipated, if pouch is > 6 cm in length or > 5 cm in width[58,59]. Although, subjects who develop large pouches (> 50 mL) may comprise comparable weight loss to those with normal sized pouches[59]. However, this never omit contribution of large pouch to weight regain[57,58].

Consequently, Dayyeh *et al*[59] found that dilated gastrojejunal stoma after RYGB produces early gastric pouch emptying, they concluded that its' diameter was correlated with weight regain. While in LSG weight regain may result from physiologic dilation of stomach remnant in the long run, or failure of complete removal of the gastric fundus[60]. This entails reduction in post-prandial satiety, allowing increased volume of food consumed, to the extent that 59% of patients regained more than 20% of their lost body weight[60,61].

Hormonal/metabolic imbalance

Summary of gut hormone changes after surgery: A chief focus after performing bariatric surgery is time interval of satiety hormones signifying early sense of fullness with smaller meals based on their release site[62]. Additionally, there is an overall agreement that great improvement in glycemic control accomplished are likely to be associated with alterations in the secretion of gastrointestinal hormones including hunger (ghrelin), satiety [glucagon-like peptide-1 (GLP-1) and peptide tyrosine tyrosine (PYY)], and energy balance[63].

LSG reduces the size of the stomach; stimulus for gut hormones secretion specifically GLP-1 is obtained by proximal alimentary signals, *e.g.,* increased cholecystokinin derived by entrance of hydrochloric acid, amino acids, or fatty acids into duodenum[64,65]. These changes influence release of ghrelin, PYY, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) as well as other gut hormones[65, 66]. On the other hand, RYGB approach, eliminates the stomach and proximal small intestine, creating a small pouch and direct connection with distal gut, consequential variations in gut hormones secretion results from abrupt exposure of intestinal epithelium to nutrients, with subsequent stimulation of L- cells[66]. This is coupled with significantly suppressed ghrelin, elevated GLP1, PYY levels, along with high pH of undigested chyme possibly contributing to diminished food intake and altered energy expenditure, leading to weight loss[66,67]. Also, exclusion of the upper segment of the intestine, where the GIP producing K-cells are present, would entail diminished levels of GIP, and is likely to constrain fat accumulation and intuitively supports long-term weight loss maintenance[68].

Hormonal disparity associated with weight regain

GLP-1: Acts to lower blood glucose by stimulating insulin release and inhibiting glucagon secretion[65]. GLP-1 is decomposed by ubiquitous dipeptidyl peptidase-IV (DPP-IV) enzyme[69]. Conversely, DPP-IV expression seems to be mediated by epigenetic influences as hyper- methylation of the DPP-IV promoter due to unhealthy lifestyle or genetic predisposition[69]. Also, deregulation of metalloproteinases coincident with fibrosis in different adipose tissue depots were found to induce insulin resistance in adipocytes and skeletal muscle cells[70]. Specifically, morbidly obese subjects coupled with insulin resistance undergoing bariatric surgery, may confront suboptimal response of GLP-1 associated with possibility of weight regain[71]. Those subjects achieve better response in terms of glycemic control and weight loss upon management with postoperative DPP-IV inhibitors[72].

Ghrelin/leptin ratio: A range of subjects may display a robust neuroendocrine-metabolic starvation feedback to initial weight loss that promotes metabolic energy preservation and favors weight regain after bariatric surgery[73]. Furthermore, Serum leptin is expected to decline by 50% after the first postoperative week, with an additional decrease during the first postoperative year[67]. Consequently, good responders revealed greater ghrelin to leptin ratio during fasting and post-prandial preoperative assessment contrasted with those who encountered weight regain[73].

On the other hand, operated patients who gradually regain weight, encountered resistance to the satiety-inducing effects of leptin[74]. The condition is characterized by elevated circulating leptin levels and decreased leptin sensitivity[75].

Growth hormone: Growth hormone (GH) is another sporadic factor principally regulated by two hypothalamic peptide hormones: GH-releasing hormone (GHRH) and somatostatin[76]. Though, further brain signaling pathways are participating in the control of GH secretion. Obese subjects may exhibit multiple endocrine defects that correspond to body composition variations, as increased visceral fat and decreased fat-free mass[77]. Theoretically, combination of various somatotropic axis alterations might be accountable for diverse scores of GH and insulin growth factor-1 (IGF-1) deficiency in obese subjects. Among the underlying neuroendocrine alterations of low plasma GH levels in obesity, associated with GHRH, somatostatin dysregulation[77]. Few studied recommended preoperative evaluations of GH/IGF-1[78]. They proposed that prevalence of persisting GH and/or IGF-1 levels below the normal range for six months after surgery was correlated with a significantly insufficient weight loss[77, 78]. The GH/IGF-1 axis is assessed by evaluating serum IGF-1 Levels and the GH peak after stimulation by (GHRH + arginine hydrochloride)[78].

Reactive hypoglycemia: Establishes another hypothesis for weight regain as a consequence of dumping syndrome, mediated by hypersecretion of GIP and GLP-1, which may induce B cell expansion and insulin hypersecretion as long term consequences[79, 80]. Besides this, Hypoglycemia ensues in 64%-82% of subjects within 5 years postoperative. The assumption for its occurrence involve refined pancreatic B cells function and mass, improved insulin sensitivity, diminished ghrelin level[80,81]. Since glucose is perceived as a chief appetite mediator, several attacks of hypoglycemia due to substantial insulin hypersecretion after meals, may trigger appetite[82]. Relatedly, direct effect of insulin on lipid accumulation since one of major function of insulin is inhibition of lipolysis[81,83]. Hence existing information reveals that attenuated postprandial gut hormone feedback /or reactive hypoglycaemia may show a correlation between eating disorders and hormonal imbalance[75,84].

Female menopause: Female menopause would apparently reduce effectiveness of bariatric-surgery outcome; given that estrogens mediate the effects of reproductive axis function on weight regulation[85]. Asarian *et al*[86] concluded that surgery seems more effective for pre-menopausal women (or post-menopausal women receiving hormone replacement therapy) than climacteric women with lower levels of estrogen. Because estrogens powerfully regulate the satiating effect of gut hormones as GLP-1 [76,85].

Genetic predisposition

Authentically, it is largely proposed that genetic and environmental aspects could modify the outcome of bariatric surgery, especially in the long run[87,88]. Exceedingly high baseline BMI > 50 kg/m^2 is be associated with concomitant fast postoperative weight loss, besides greater risk of postoperative weight regain[89,90].

Numerous genes were identified as obesity related genes, and mutations of any produces rare monogenic forms predispose to obesity; including leptin gene, leptin receptor, pro-opiomelanocortin (POMC), melanocortin 4 receptor, melanocortin 3 receptor, fat mass and obesity-associated (FTO), insulin induced gene 2, G protein-coupled receptor 24, corticotropin releasing hormone receptor and corticotropin releasing hormone receptor[91]. Remarkably, mutations in the zone of leptin/melanocortin pathway in the central nervous system being essential in regulation of energy homeostasis appears to result in enhanced appetite and reduced satiety, consequently early postoperative failure[89].

Accordingly, generation of genome-wide association studies (GWAS) provides a reasonably rich source of information to illustrate the molecular mechanisms connecting gene regulation, lifestyle and environmental factors in defining the risk of obesity[92,93]. Thus GWAS has improved comprehension of common genetic variants and collectively elucidated approximately 6% of the variation in adult BMI[93,94]. Correspondingly, the current hypothesis asserts that patients carrying none or few number of risk alleles of obesity show more efficient weight loss after bariatric surgery than carriers of multiple risk variants[95]. Genetic risk scores is computed by summarizing risk related variants across the genome, through gathering information from various predictive single nucleotide polymorphism (SNP)[91].

Unfortunately, in spite of intensive genetic research, the molecular mechanisms are barely clarified[91,95]. The epigenetic alterations preceding or post-translational regulatory genes without changes in the nucleotide sequence, particularly methylation of DNA cytosine (C) represents an extremely stable modification[96]. Particularly epigenetic markers, in subjects who regained the weight loss induced by nutritional or surgical intervention displayed differential DNA methylation patterns in leukocytes or subcutaneous adipose tissue or compared to subjects successfully maintained their weight loss over a short or long periods[97].

Eventually, the methylation of genes involved in metabolic pathways exhibited changes after bariatric surgery. For example, weight regain is associated with hyper methylation of POMC and in turn, revealed higher melanocyte stimulating hormone-positive neurons[97]. On the other side, low methylation of neuropeptide Y gene is linked to hunger and satiety controlling peptides as ghrelin[98]. Furthermore, distinctive variants of FTO gene interrelate with dietary subscription, as high-protein regime benefits weight loss and improvement of body configuration in carriers of the FTO risk allele rs1558902, while carriers of FTO rs9939609 allele attained better weight loss response to low-fat hypocaloric diet[99].

Another epigenetic element is small non-coding RNAs (21-22 nucleotides), they are crucial for post-transcriptional regulation of gene expression. Single-stranded micro-RNA (miRNA) binds to a complementary target messenger RNA (mRNA) to disrupt translational processes[100]. Some studies reported short- and long-term miRNA profile changes after bariatric surgery in diverse tissues of both animal and humans that were associated with weight regain/or failure to achieve the desired body weight [101,102]. Accordingly, Obesity provoked changes in miRNA concentration within adipose tissues which promotes chemotaxis of macrophages and other immune cells towards the adipocytes. These miRNAs further impose chronic low grade inflammation, which sequentially may alter miRNA profile[103]. For example, miR-365 and miR-574, are proposed in adipose tissue hypertrophy through regulation of Early B cell factor 2 specific brown fat selective role involved in adipocyte differentiation *via* regulation of Peroxisome proliferator-activated receptor Gamma PPARγ, a ligand-activated transcription factor, involved in numerous cellular functions as lipid metabolism, glucose homeostasis and impediment of oxidative stress[104]. Therefore, they may represent prospective targets for non-surgical therapy of obesity and postulate novel biomarkers for predicting bariatric surgery outcomes[103].

PREDICTORS OF WEIGHT REGAIN

An essential measure during evaluation of patients with obesity prior to surgery; is identification of attributes or biomarkers that could deduce improvement of the metabolic profile of candidates that benefits from surgery on long term. Also, to categorize subjects more susceptibility to regain weight after surgery[32].

A greater weight reduction during early weight loss phase postoperative

Initial prosperous weight loss within the first few months postoperative anticipated long term weight loss at 4 and 8 years, examining long-term impression of intensive lifestyle intrusion on obesity associated comorbidities and mortality[35,105]. Also, Vogels *et al*[106] assumed that comparatively high baseline BMI and fat mass were correlated with concomitant long-term weight loss maintenance during two years follow up period (< 10% regain). Alvarado *et al*[107] deduced better response upon requesting morbidly obese subjects to lose around 4.5-9 kg of weight, in few weeks instantaneously prior to bariatric surgery, they attained improved postoperative weight loss. Similarly, some studies assessed preoperative weight loss of less than 5% or 5%-10% of total body weight was accompanied with superior outcome[108,109], However, other studies concluded that extremely high baseline BMI above 50 kg/m^2 was correlated with inferior postoperative weight loss (below 50% EWL)[110,111].

Baseline insulin sensitivity

Insulin regulates numerous metabolic processes within serval organ in body. Consequently, reduced sensitivity to insulin action is termed insulin resistance, *i.e.*, suboptimal response of various metabolic functions to normal insulin levels in blood [112]. It has a prime influence in predicting vulnerability to weight regain, and may be concluded through insulin resistance as defined by HOMA-IR[113]. Hence high baseline plasma insulin may be indicative of postoperative insulin resistance[112]. Similarly, Antuna-Puente *et al*[114] proposed that subjects with high plasma triglyceride concentrations were found to be insulin resistant. Kong *et al*[115] recommended applying a combination of biomarkers including elevated baseline fasting plasma insulin and inflammatory biomarkers as IL-6 levels, and the number of HAM56^{+} cells (macrophages) in subcutaneous white adipose tissue (WAT) to anticipate opposition to weight loss as well as susceptibility to weight regain with a prediction accuracy of 75%. Estimation of pancreatic β cell function (insulin secretion) and insulin sensitivity were calculated by using following formulas[116,117]:

(1) HOMA-IR = [Fasting insulin (uU/mL) × Fasting blood glucose (nmol/L)]/22.5.

(2) HOMA-β = [20 × fasting insulin (uU/mL)]/[Fasting blood glucose (mmol/L)-3.5].

(3) Quantitative insulin-sensitivity check index (QUICKI)= 1/[log fasting plasma insulin (uU/mL) + log fasting blood glucose(mg/dL)].

(4) Oral glucose tolerance test (OGTT): Fasting blood samples are drawn, then subject ingest 75 gm glucose load for OGTT. Glucose and insulin are measured in all blood samples obtained, usually at 0, 60, and 120 min or only 0 and 120 min during the OGTT.

(5) Matsuda index = 10000√ (FPI × FPG) × (x GPC × x IPC). Where FPI is fasting plasma insulin expressed as μU/mL, FPG is fasting plasma glucose expressed as mg/dL, x GPC is mean plasma glucose concentration after the load and x IPC is the mean insulin concentration after the load[117].

Expected normal ranges for above parameters: HOMA-IR normal range is less than 1.4, HOMA-β reference value is less than 81.7, while QUICKI index is less than 0.4 and MATSUDA index non diabetic range is less than 4.5[116,117].

Plasma concentrations of total cysteine

Plasma cysteine level is strongly connected with enlarged fat mass, probabilities of developing obesity and could be used as predictor of weight regain[118,119]. Cysteine is an essential sulfur-containing amino acid, that can form disulfide linkages, which simultaneously regulate protein structure and stability[120]. Circulating total cysteine (tCys) exists either as free cysteine homogeneous (cystine) or mixed (*e.g.*, homocysteine-cysteine) disulfides, and albumin-bound cysteine[121]. While cellular cysteine is the rate limiting precursor of intracellular antioxidant glutathione and prevail principally in reduced form[122]. Since plasma tCys is predominantly oxidized, high levels tCys, presume unfavorable outcomes, and is often related to obesity[120].

In addition, Cysteine enhances the activity of stearoyl-CoA desaturase-1 (SCD-1), which is a key enzyme for synthesis of monounsaturated fatty acids. SCD-1 introduces a single double bond at the Δ9, 10 of long-chain acyl-CoA substrates[123]. Its chief products are palmitoleic acid and oleic acid; the largely copious fatty acids in cholesterol esters, membrane phospholipids and triglycerides[123]. The activity of SCD-1 is also associated with the levels of sulfur containing amino acid, particularly cysteine. So SCD-1 suppression results in diminished fat deposits (regardless of food intake), enhanced insulin sensitivity and greater basal energy expenditure[123,124]. Accordingly, high plasma tCys observed to be positively linked to elevated total cholesterol, low density lipoprotein-cholesterol and triglycerides[125]. As it effectively inhibits hormone-sensitive lipase, and promotes adipocyte triglyceride and glucose uptake[125]. Hanvold *et al*[126] concluded that profound tCys elevation two years after RYGB was associated with weight regain.

Plasma adipokines

Some adipokines have displayed the ability to influence weight regain owing to their roles in energy expenditure and or food intake as adiponectin, retinol-binding protein 4 (RBP4), angiotensin converting enzyme (ACE) activity[127].

RBP4: RBP4 is transport protein for retinol (Vitamin A) secreted mainly by the liver and to a lesser extent by the adipose tissue. Munkhtulga *et al*[128] stated that the minor allele of regulatory RBP4 SNP was found to augment adipocyte RBP4 expression and was correlated with elevated BMI in Asian population. Wang *et al*[129] reported higher baseline RBP4 associated with compromised weight loss, they elucidated increased release of RBP4 in obese WAT owing to the presence of hypertrophic adipocytes during weight regain. In view that RBP4 carrying retinol is a precursor of ligands of retinoid X receptor, which activates peroxisome proliferator activated receptors modulating transcription of genes involved in fat metabolism and adipogenesis[130]. In this respect, elevated RBP4 level reflects stimulated adipocyte proliferation, adipogenesis and accordingly weight regain[131].

Additionally, RBP4 Links to insulin resistance through RBP4 associated effects comprising increased hepatic gluconeogenesis by accentuating the exhibition of phosphoenolpyruvate carboxykinase enzyme in the liver which simultaneously suppresses insulin signaling in skeletal muscle by blocking insulin-stimulated phosphorylation of insulin receptor substrate-1[132]. Moreover, glucose transporter GLUT4 protein level in human adipocytes correlates positively with the rate of glucose clearance and inversely with circulating RBP4 level[133].

ACE: ACE gene polymorphisms are associated with BMI and obesity[134]. Provided that immense amounts angiotensin II (Ang II), product of ACE activates adipocyte differentiation and consequently influence adipose tissue mass[135]. Moreover, Wang *et al*[136] observed that greater reduction in ACE level was coupled with stable body weight during follow-up and abstained tendency to weight regain. Velkoska *et al*[137] demonstrated the effect of ACE inhibitors on body weight management by reducing body water or *via* reduction in energy intake.

ACE is a carboxypeptidase that is expressed in many tissues including adipose tissue but predominantly in the vascular endothelium, brain and lung. The enzyme is anchored to cell membranes and is shed into the plasma by enzymatic cleavage[138]. Furthermore, a positive association between the weight loss induced change in serum ACE concentration and weight regain during *ad libitum* feeding (free feeding)[138, 139]. A causal association appears between ACE and weight regain. However, the underlying mechanism remains unclear, in spite of the fact that ACE plays a role in many processes other than the regulation of blood pressure, such as inflammation, fibrosis and the regulation of food intake by the hypothalamus by reinforcing thermogenesis (though corticotrophin releasing hormone-autonomous mechanism)[136].

Fibroblast growth factor 21: Fibroblast growth factor 21 (FGF21) is a "myokine." that stimulates the oxidation of fatty acids, production of ketone bodies, and inhibition of lipogenesis[141]. Kharitonenkov *et al*[141] proposed that it could be a prospective metabolic regulator and a potential anti-diabetic drug. FGF21 mRNA is expressed in gastrointestinal tract, brain, skeletal muscle, brown adipose tissue, and heart[142]. FGF21 is a molecule with a very short half-life of 1-2 h in absence of specific stimuli, due to enzymatic cleavage by fibroblast activation protein α (FAP), a serine protease that inactivates FGF21[143]. Interestingly, FAP is secreted from muscle during physical exercise[144]. Also, FGF21 is removed from circulation by renal clearance[140].

FGF21 acts as a fasting-induced hormone intended for the adaptive response to starvation and consumption of energy derived from tissues breakdown[145]. Several studies hypothesized relationship between energy expenditure, body weight regulation and FGF21[145-147]. Through provoking energy expenditure with acute low-protein diet 3% causes almost an average energy expenditure (adaptive thermogenesis) can identify individuals who are able to disperse the excess calories consumed as heat ("spendthrift") opposed to those who are incapable ("thrifty")[145]. The extent of the elevation in serum FGF21 level in condition of acute low-protein overfeeding is positively correlated with the acute change in 24-h energy expenditure. While poor responders (Thrifty) show an attenuated FGF21 response to acute low-protein feeding, therefore are vulnerable to weight gain over 6 mo[145,146]. Provided that individuals don't suffer liver, cardiac, kidney or muscle disease which may interfere with test results[147].

CONCLUSION

Bariatric surgery is a tool to achieve significant weight loss, to obtain maximum benefit must adapt pre and postoperative follow up. Also, the role of a nutritionist in bariatric surgery team has expanded ahead diet counseling, to address individual barriers and counsel morbidly obese subjects by ensuring they understand selected bariatric procedures, offering education, identify individual factors that may predict weight regain, reinforce self-monitoring skills, encourage mindful eating practices, supply appropriate nutritional supplements, and motivate daily physical activity, provide close support and follow-up to avoid relapse.

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MINIREVIEWS

Review of the effects of SARS-CoV2 infection and COVID-19 on common pediatric psychiatric illnesses

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Abstract

Severe acute respiratory syndrome coronavirus-2 is a novel coronavirus strain that causes pneumonia and acute respiratory distress syndrome along with other morbidities, collectively known as coronavirus disease 2019 (COVID-19) disease. There has been widespread discussion about the psychological impact of COVID-19 particularly on children and adolescents. There have been overarching negative effects with regards to decreased physical activity, more screen time, increasingly unhealthy diets, and irregularities in sleep/wake schedules. This, coupled with disruptions in ongoing mental health treatment and associated support structures, has caused unprecedented declines in the emotional and psychosocial wellbeing of children and adolescents. This review aims to systematically review the literature to provide a general overview of the ways in which COVID-19 has affected common psychiatric illnesses in children and adolescents. The included articles in all subsections concluded that symptoms of these common childhood psychiatric disorders have generally been exacerbated by the COVID-19 pandemic. This review indicates that quarantine and the consequent isolation have had multiple significant and consistent negative implications on the mental health of children and adolescents. Our study indicates that there should be increased vigilance among providers and families to mitigate the negative psychological effects that the COVID-19 pandemic has on children with common childhood psychiatric disorders.

Key Words: COVID-19; Depression; Anxiety; Attention deficit hyperactivity disorder; Obsessive-compulsive disorder; Tourette's; Children; Adolescents

Core Tip: The included articles in all subsections concluded that symptoms of these

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common childhood psychiatric disorders have generally been exacerbated by the coronavirus disease 2019 (COVID-19) pandemic. Our study indicates that there should be increased vigilance among pediatricians and families to mitigate the negative psychological effects that the COVID-19 pandemic has on children with common childhood psychiatric disorders. This calls out for pediatricians, psychiatrists, and all providers alike to remain cognizant of these effects and work collaboratively towards measures to reduce the psychological impact of COVID-19.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), is a novel coronavirus strain that causes pneumonia and acute respiratory distress syndrome along with other morbidities, collectively known as coronavirus disease 2019 (COVID-19) disease [1]. The World Health Organization declared SARS-CoV2 infection to be a global pandemic in March 2020. As of February 2021, there are upwards of 110 million cases of SARS-CoV2 infection worldwide with over 28 million cases and 500000 total deaths documented in the United States. In addition to significant medical impact, there has also been a profound psychologic impact because of the pandemic, particularly among vulnerable populations. There has been widespread discussion about the psychological impact of COVID-19 particularly on children and adolescents[2].

Since the start of the pandemic, the transition to online-based education, increasing school closures, and the alteration of normal adolescent social activities have caused an unmitigated disruption in the lives of children[2]. In general, the greatest impacts appear to be losses in areas of daily routine, institutional support structures, and social connection[2]. Though these effects are generally attributed to the cessation of in-person learning in schools, it is generally assumed that there have been overarching detrimental effects with regards to decreased physical activity, more TV and screen time, increasingly unhealthy diets, and irregularities in sleep/wake schedules[2].

This, coupled with disruptions in ongoing mental health treatment and associated support structures, has caused unprecedented declines in the emotional and psychosocial wellbeing of children and adolescents[2].

This review aims to systematically review the literature to provide a general overview of the ways in which COVID-19 has affected common psychiatric illnesses in children and adolescents.

For this review, we performed multiple literature searches of PubMed, Cochrane and PsycInfo to find articles (Figures 1-5). The first search used the keywords "COVID 19," "children," and "OCD," the second search used the keywords "COVID 19," "children," and "ADHD," the third search used the keywords "COVID 19," "children," and "Tourette's syndrome," the fourth search used the keywords "COVID 19," "children," and "depression," and the fifth search used the keywords "COVID 19," "children," and "anxiety." The search was not initially restricted by study design or language but was limited to articles published between January 1 to December 31, 2020. Review articles published in or translated to English were included. Full-text references cited in these articles were also researched for additional relevant studies. The inclusion criteria were on-topic articles discussing the effect of COVID-19 on common pediatric psychiatric disorders. The exclusion criteria were any study designs that were case reports, surveys, or study protocols, or articles that were considered to be off topic.

OBSESSIVE COMPULSIVE DISORDER

A total of 12 articles were identified through a literature search. There were no clinical

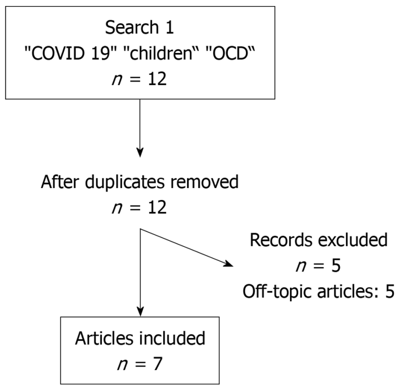
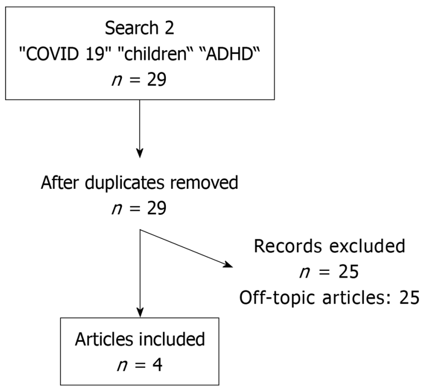


Figure 1 PRISMA table for Search 1.



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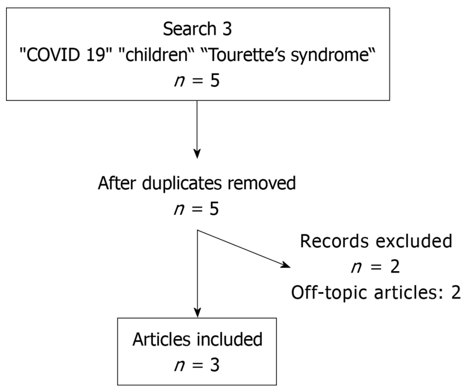
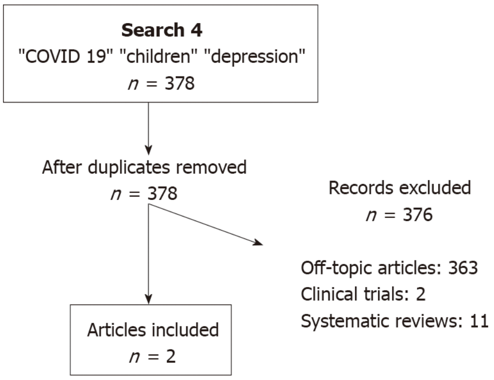


Figure 3 PRISMA table for Search 3.

trials, randomized controlled trials or meta-analysis that were identified. After excluding articles that were off-topic, seven articles remained for inclusion (Figure 1).

Though the mean age of onset for those with obsessive-compulsive disorder (OCD) is 19.5 years, childhood onset does occur and generally persists throughout adulthood [3]. According to the diagnostic and statistical manual of mental disorders, 5th edition, 25% of males have onset of symptoms before age 10. Characterized by obsessions and compulsions, OCD can present with a varying combination of symptoms including intrusive and persistent unwanted thoughts, repetitive checking, fears of contamination, feelings of worry and disgust, and repetitive behaviors or patterns of behaviors that an individual is compelled to perform[4,5]. In general, symptoms of OCD are exacerbated by acute stressors, such as trauma.

Due to the COVID-19 pandemic, children and adolescents who are susceptible to OCD are most likely to be affected[6]. There were several studies that concluded that children and adolescents diagnosed with OCD experienced a considerable worsening



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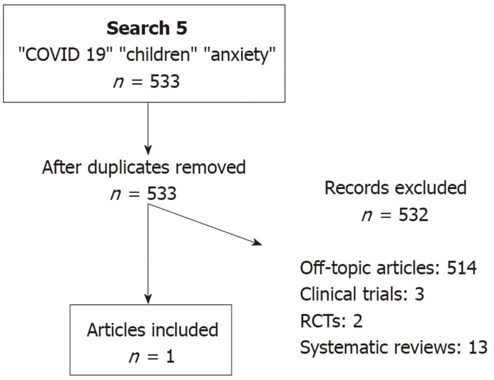

Figure 5 PRISMA table for Search 5.

of their symptoms[6-10]. One particular study concluded that this significant worsening was most prevalent in those with an earlier age of symptom onset and in those with a family history of attention deficit hyperactivity disorder (ADHD)[7]. Another study also identified a substantial increase in contamination fears and cleaning or washing obsessions due to general fears of exposure to infection brought on by the pandemic[8,9]. Contrastingly, there has also been widespread advocacy of infection control measures, such as frequent handwashing, and dissemination of information on avoiding exposure/contamination. These measures may actually lead to those suffering from severe OCD symptoms to feel less stigmatization over their cleansing obsessions[9,10]. They may instead feel more acceptance over their symptoms, as their fears become well-founded and "real" and their ritualized behaviors became generally widespread and even encouraged[9,10]. Therapeutic interventions, such as cognitive behavioral therapy, are designed to achieve symptomatic relief by targeting behaviors like excessive hand washing and intrusive thoughts of contamination. This can lead to a cognitive dissonance in those with OCD as the COVID-19 pandemic has led to a widespread and public campaign to encourage these behaviors.

ADHD

A total of 29 articles were identified through a literature search. There were no clinical trials, randomized controlled trials or meta-analysis that were identified. After excluding articles that were off-topic, four articles remained for inclusion (Figure 2).

ADHD, characterized by persistent patterns of inattention and/or hyperactivity/impulsivity that interferes with functioning, is one of the most prevalent psychiatric disorders of childhood[3,11]. In general, children diagnosed with ADHD have been noted to experience an exacerbation of symptoms throughout the COVID-19 pandemic[11-14]. In addition, children with the hyperactive phenotype of ADHD may find the constraints of quarantine and lockdown to be particularly difficult to accommodate[15]. Several studies noted an increase in symptoms such as hyperactivity, irritability, emotional outbursts, and defiant or disruptive behavior[12-14]. There was also a noted increase in problematic behaviors from caregivers, such as irritability or aggressive behavior directed towards the child. These changes were generally attributed to both the nonspecific emotional stress caused by the pandemic and the lack of daily structure and increasingly flexible school/Learning schedules [13].

TOURETTE'S DISORDER

A total of five articles were identified through a literature search. There were no clinical trials, randomized controlled trials or meta-analysis that were identified. After excluding articles that were off-topic, three articles remained for inclusion (Figure 3).

Public health measures aimed at controlling the spread of the COVID-19 pandemic have led to some changes in the symptomatic presentation of Tourette's disorder[15-17]. The advent of online learning and social distancing measures have decreased the social burden of tics, and resulting psychological distress, felt by children in school and other learning environments[16]. In contrast, several other non-obscene socially inappropriate tics - such as spitting, coughing, sneezing, or inability to maintain interpersonal distance with touching – have become more socially unacceptable[15]. This can lead to increased anxiety and distress in children with these symptoms who may feel undue pressure to modify or control these behaviors[15]. This increased anxiety can lead to a secondary increase in tic symptoms[15]. In general, children with Tourette's disorder were observed to have overall clinical decline with either a worsening of existing symptoms or a resurgence of previously-controlled symptoms [15-17].

DEPRESSION AND ANXIETY

A total of 378 articles were identified through a literature search by using the keywords "COVID," "depression," and "children." There were two clinical trials, two meta-analysis, and eleven systematic reviews. There were no randomized controlled trials that were identified. The clinical trials were excluded as they were off topic. The systematic reviews were excluded due to the overlap from within the meta-analyses. After excluding articles that were off-topic, two meta-analyses remained for inclusion (Figure 4).

A total of 533 articles were identified through a literature search by using the keywords "COVID," "anxiety," and "children." There were three clinical trials, four meta-analysis, two randomized controlled trials, and thirteen systematic reviews. The clinical trials were excluded as they were off topic. The randomized controlled trials were excluded as they were not pertinent to the population subgroup of our review and dealt with the ailments in the adult population. The systematic reviews were excluded due to the overlap from within the meta-analyses. After excluding articles that were off-topic, one meta-analysis remained for inclusion (Figure 5).

Both anxiety and depression are major ailments amongst the youth that are often under-reported and under-recognized. Data by SAMHSA, or the Substance Abuse and Mental Health Services Administration, shows that the overall prevalence of depression for adolescents aged 12 to 18 is 13.1% as opposed to 7.1% for adults. Similarly, the rates are 31.9% and 19.1% when it comes to anxiety amongst adolescents, and adults respectively. This means that the relative prevalence of these disorders already remains higher amongst the adolescents as compared to adults.

COVID-19 and its consequent effects have further negatively impacted the mental health of children and adolescents. Multiple studies have shown that social isolation and the resultant loneliness were associated with increased risk of both depression and anxiety[18-25]. Anxiety was seen to be more prevalent amongst children maintaining quarantine, and this was thought to be likely mostly due to loss of primary caregiver's job, financial instability leading to a dearth in provision of basic amenities[22]. It was also noted that the time period of isolation was more important for symptomatology of mental health ailments than the severity of isolation[23].

The studies noted certain interesting factors. There was seen to be a mild difference between the sexes as well, with loneliness being more strongly associated with social anxiety in boys and depression in girls[23]. Certain primary school students who viewed COVID-19 as a serious disease had increased anxiety and somatic symptoms [2]. One study mentioned that children who practiced social distancing for fear of getting infected were predisposed to anxiety disorders. The same study also mentioned that children who engaged in social distancing secondary to peer pressure had a higher likelihood of depression[24]. This illustrates a thought-provoking difference in symptoms based upon the motivator for social distancing in the first place. Interestingly an age-related difference was also discernible in certain study populations. High school children reported higher number and severity of symptoms of anxiety and depression as compared to their primary and middle school counterparts[24,25]. Certain salient causes of increased depression levels in the study population were also noticed such as internet/smartphone addiction and affected friends/family members in the past.

On the contrary a few of the factors protective towards depression were lesser time spent on the internet, adequate coping mechanisms, increased exercise time, and having a sibling[19,20]. It should come as no surprise that the pandemic meant more children/adolescents, and adults alike ended up spending increased time on the internet and lesser time outdoors. Similarly, children and adolescents with worry and fear about COVID-19 had higher rates of depression, whereas remaining optimistic amidst these times had the opposite effect[2].

CONCLUSION

The included articles in all subsections concluded that symptoms of these common childhood psychiatric disorders have generally been exacerbated by the COVID-19 pandemic. This was primarily attributed to the restricting quarantining regulations and the public fear of SARS-CoV2 infection. For instance, the routine learning schedule implemented at public schools that had helped to provide structure to children with ADHD have been lost while quarantining at home. This in turn led to worsening ADHD symptoms and behaviors. The public fear of COVID-19 and the widespread encouragement of frequent handwashing have both exacerbated contamination fears in those with OCD experience and worsened repetitive sanitizing behaviors. While children with Tourette's Disorder may have experienced less psychosocial distress over their tics by being away from school, they may still face difficulties with controlling symptoms because of increased anxiety over their tic behaviors breaking social-distancing rules.

This review portends that quarantine and the consequent isolation have had multiple significant and consistent negative implications on the mental health of children and adolescents. The stigmata of these consequences can be detected even months later beyond quarantine[25]. In general, a lack of vigilance and treatment for pandemic-associated effects on childhood psychiatric disorders may propagate significantly negative and refractory long-term sequelae into adulthood. Our study indicates that there should be increased vigilance among clinicians and families to mitigate the negative psychological effects that the COVID-19 pandemic has on children with common childhood psychiatric disorders. This calls for pediatricians, psychiatrists, and all healthcare providers alike to remain cognizant of these effects and work collaboratively towards measures to reduce the psychological impact of this already menacing physical ailment.

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META-ANALYSIS

Maturation of robotic liver resection during the last decade: A systematic review and meta-analysis

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Author contributions: Ishinuki T and Ota S developed the study concept and designed the systematic review; Ishinuki T, Meguro M, and Ohyanagi T searched for and screened the articles; Kawamoto M, Harada K, and Tatsumi H assessed the articles for eligibility; Miyanishi K carried out the statistical analyses; Takemasa I supervised and audited the preparation of the manuscript; Hui TT and Mizuguchi T drafted the initial manuscript; Mizuguchi T finalized the manuscript; All of the authors reviewed and approved the final submitted manuscript.

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Abstract

BACKGROUND

Minimally invasive hepatectomy techniques have developed rapidly since 2000.

Pure laparoscopic liver resection (LLR) has become the primary approach for managing liver tumors and procuring donor organs for liver transplantation. Robotic liver resection (RLR) has emerged during the last decade. The technical status of RLR seems to be improving.

AIM

To conduct a systematic review and meta-analysis comparing the short-term clinical outcomes of LLR and RLR over two 5-year periods.

METHODS

A systematic literature search was performed using PubMed and Medline, including the Cochrane Library. The following inclusion criteria were set for the meta-analysis: (1) Studies comparing LLR *vs* RLR; and (2) Studies that described clinical outcomes, such as the operative time, intraoperative bleeding, intraoperative conversion rate, and postoperative complications.

RESULTS

A total of 25 articles were included in this meta-analysis after 40 articles had been subjected to full-text evaluations. The studies were divided into early (n = 14) and recent (n = 11) groups. In the recent group, the operative time did not differ significantly between LLR and RLR (P = 0.70), whereas in the early group the operative time of LLR was significantly shorter than that of RLR (P < 0.001).

CONCLUSION

The initial disadvantages of RLR, such as its long operation time, have been overcome during the last 5 years. The other clinical outcomes of RLR are comparable to those of LLR. The cost and quality-of-life outcomes of RLR should be evaluated in future studies to promote its routine clinical use.

Key Words: Hepatectomy; Laparoscopy; Robot; Operation time

Core Tip: A systematic review and meta-analysis comparing the clinical outcomes of laparoscopic liver resection (LLR) and robotic liver resection (RLR) was conducted. A total of 25 studies were included in the meta-analysis. In the recent studies, operative time did not differ significantly between LLR and RLR (P = 0.70), whereas in the early studies LLR was associated with significantly shorter operative times than RLR (P < 0.001). The initial disadvantages of RLR have been overcome during the last 5 years.

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INTRODUCTION

Surgery is a curative treatment for liver tumors[1]. The development of surgical devices has promoted minimally invasive surgery (MIS), including minimally invasive liver resection[2]. Therefore, the concept of 'big surgeons, big incision' has become a myth[3]. Minimal skin wounds are preferable, and patients who undergo laparoscopic liver resection (LLR) recover faster without somatic pain than those that undergo open liver resection[1,4].

MIS has significant clinical benefits, *e.g.*, it results in faster recovery, less pain, and shorter hospital stays[5]. On the other hand, long operation times and the associated higher costs were reported as disadvantages of the MIS approach[4,5]. However, the disadvantages of the MIS approach might be ameliorated as surgeons gain experience

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[6]. Initially, LLR was reported to have various clinical benefits but result in longer operation times[4].

Robotic surgery has gained popularity since 2000[7]. Although robotic towers occupy space in the operating room, the skill of surgeons can be enhanced by robotic technology, such as "wristed instruments", "tremor cancellation", "enhanced dexterity", and "3D vision"[8,9]. These technologies are considered to reduce 93% of errors associated with human skill[8].

Total robotic liver resection (RLR) is limited to minor liver resection, which does not require the liver to be mobilized[10]. Furthermore, the robotic approach is only used for parenchymal dissection during laparoscopic surgery[11]. Therefore, the clinical outcomes of LLR and RLR should be similar[5,12]. We systematically reviewed the literature in which the clinical outcomes of LLR and RLR were compared. We divided the studies according to the year of publication to determine how the clinical outcomes of these techniques have changed over time. Early studies were defined as those published in 2016 or earlier. Recent studies were defined as those published in 2017 or later. We also examined the current status of RLR through a meta-analysis.

MATERIALS AND METHODS

Literature search

The Preferred Reporting Items for Systematic Reviews And Meta-Analyses (PRISMA) statement guidelines were followed when obtaining and reporting the meta-analysis data[13]. The PICOS scheme was employed when reporting the inclusion criteria. A systematic literature search of PubMed and MEDLINE, including the Cochrane Library, was performed independently by two authors (Ishinuki T and Ota S). The search was limited to human studies whose findings were reported in English. No restriction was set with regard to the type of publication, the publication date, or publication status. Patients of any age or sex who underwent liver resection for any hepatic lesion were considered, as outlined in the PICOS scheme. The search strategy was based on different combinations of words for each database. For the PubMed database the following combination was used: ("hepatectomy"[MeSH Terms] OR "hepatectomy"[All Fields] OR ("liver"[All Fields] AND "resection"[All Fields]) OR "liver resection"[All Fields]) AND ("laparoscopie"[All Fields] OR "laparoscopy"[MeSH Terms] OR "laparoscopy"[All Fields] OR "laparoscopies"[All Fields]) AND ("robot"[All Fields] OR "robot s"[All Fields] OR "robotically"[All Fields] OR "robotics"[MeSH Terms] OR "robotics"[All Fields] OR "robotic"[All Fields] OR "robotization"[All Fields] OR "robotized"[All Fields] OR "robots"[All Fields]). For the MEDLINE database, including the Cochrane Library database, the following combination was used: #1. liver.mp. [mp=title, abstract, full text, caption text], #2. resection.mp. [mp=title, abstract, full text, caption text], #3. robot.mp. [mp=title, abstract, full text, caption text], #4. 1 and 2 and 3.

Selecting policy of the studies

The independent authors have read the primary studies searched in the database. Similar studies and unrelated studies were excluded. The inclusion criteria for the statistical analysis were following: (1) Studies comparing LLR and RLR; (2) Studies reporting at least one clinical result or variable; and (3) If any institution reported multiple studies, only the recent and the excellent study was selected. The policies of the exclusion were following: (1) The studies dealing with liver transplantation; (2) Reviews, opinions, comments, letters, and case reports; and (3) The studies were impossible to reproduce. The Cohen kappa statistic was used to quantify assess the agreement among the researchers.

PROSPERO was used for the protocol registration (#CRD42021234405).

Data extraction

The independent authors extracted the following initial data: (1) The name of authors, year, and quality of study; (2) The etiology of the disease; and (3) The period of the evaluations.

Bias assessment

The publication bias was assessed by the Newcastle–Ottawa Scale: NOS (http://www.ohri.ca/), as they included observational studies. The NOS consists of domains for the patient selection, comparability of study groups, and outcome

Table 1 Frequency of each type of liver resection in the studies published in 2016 or earlier

Ref.		Laparoscopic liver resection					Robotic liver resection				
		Seg	LLS	LH	RH	EH	Seg	LLS	LH	RH	EH
Berber *et al*[17], 2010	Case	12	11				6	3			
Ji *et al*[18], 2011	Case	9	7	3	1		1	4	6	2	1
Lai *et al*[19], 2011	Cohort	6	4				6	3			
Lai *et al*[20], 2012	Cohort	9	8				12	17	2	1	
Packiam *et al*[21], 2012	Case		18					11			
Troisi *et al*[9], 2013	Case	149	39	16	17	2	38	2			
Spampinato *et al*[22], 2014	Case			9	15	1			8	16	1
Tranchart *et al*[23], 2014	Case	22	5	1			22	5	1		
Tsung *et al*[12], 2014	Case	72		21			36		21		
Wu *et al*[24], 2014	Case	28	31	8	2		8	24	7	12	1
Yu *et al*[25], 2014	Case		6	11				10	3		
Croner *et al*[26], 2016	Case	ND					ND				
Kim *et al*[27], 2016	Case		31					12			
Lai *et al*[28], 2016	Cohort	25	9		1		45	29	6	20	1
Lee *et al*[29], 2016	Case	34	30	2			17	39	10	4	
Montalti *et al*[30], 2016	Case	72					36				

EH: Extended hemi-hepatectomy; LH: Left hepatectomy; LLS: Left lateral segmentectomy; ND: Not properly described; RH: Right hepatectomy; Seg: Segmentectomy.

assessment. The low risk of bias results in a score of 9 points. We considered studies that scored ≥ 7, 4-6, and < 4 to be high, moderate, and low quality, respectively[14].

Statistical analyses

RevMan software (version 5.3.; The Cochrane Collaboration) was used for the meta-analysis. For continuous variables, the differences between groups were compared using the inverse-variance method. On the other hand, dichotomous outcomes were compared using the Mantel-Haenszel method. The Egger's test for publication bias was performed using EZR (version 1.54; https://www.softpedia.com/get/Science-CAD/EZR.shtml)[15].

The χ^2 test was used to evaluate heterogeneity, and the Cochran Q and I^2 statistics were reported. The I^2 value describes the percentage variation between studies in degrees of freedom. Low, moderate, and high heterogeneity were defined based on cut-off values of 25%, 50%, and 75%, respectively[16].

All results were considered significant at P values of < 0.05.

RESULTS

The PRISMA flow diagram for this study is shown in Figure 1. The database search for relevant studies resulted in 1,068 studies being identified. We excluded 922 studies because of duplication, and the titles and abstracts of the remaining 148 studies were screened. As a result, we reviewed 40 full-text articles to evaluate their eligibility further. We excluded 8 studies for which the outcome involved a non-target comparison, and 4 studies for which the data were not available. Finally, we included 28 studies in our meta-analysis.

The data regarding the frequency of each type of liver resection in the selected studies are shown in Tables 1 and 2. Table 1 shows the data for the studies published in 2016 or earlier[9,12,17-30]. Table 2 shows the data for the studies published in 2017 or later[31-42]. No randomized controlled trials (RCT) comparing the clinical outcomes of LLR and RLR were identified. All of the selected publications related to observa-

Table 2 Frequency of each type of liver resection in the studies published in 2017 or later

Ref.		Laparoscopic liver resection					Robotic liver resection				
		Seg	LLS	LH	RH	EH	Seg	LLS	LH	RH	EH
Efanovet al[31], 2017	Cohort	ND					ND				
Magistriet al[32], 2017	Case	24					14	6		2	
Salloumet al[33], 2017	Case	ND					ND				
Fruscioneet al[34], 2019	Case	48		22	46		17		20	20	
Marinoet al[35], 2019	Cohort				20					14	
Huet al[36], 2019	Case		54					58			
Leeet al[37], 2019	Case		7	3				8	5		
Limet al[38], 2019	Case	ND					ND				
Wanget al[39], 2019	Case			29	19				48	44	
Chonget al[40], 2020	Case	47	40	3	1		34	39	12	6	
Mejiaet al[41], 2020	Case	ND					ND				
Rahimliet al[42], 2020	Case	ND					ND				

EH: Extended hemi-hepatectomy; LH: Left hepatectomy; LLS: Left lateral segmentectomy; ND: Not properly described; RH: Right hepatectomy; Seg: Segmentectomy;.

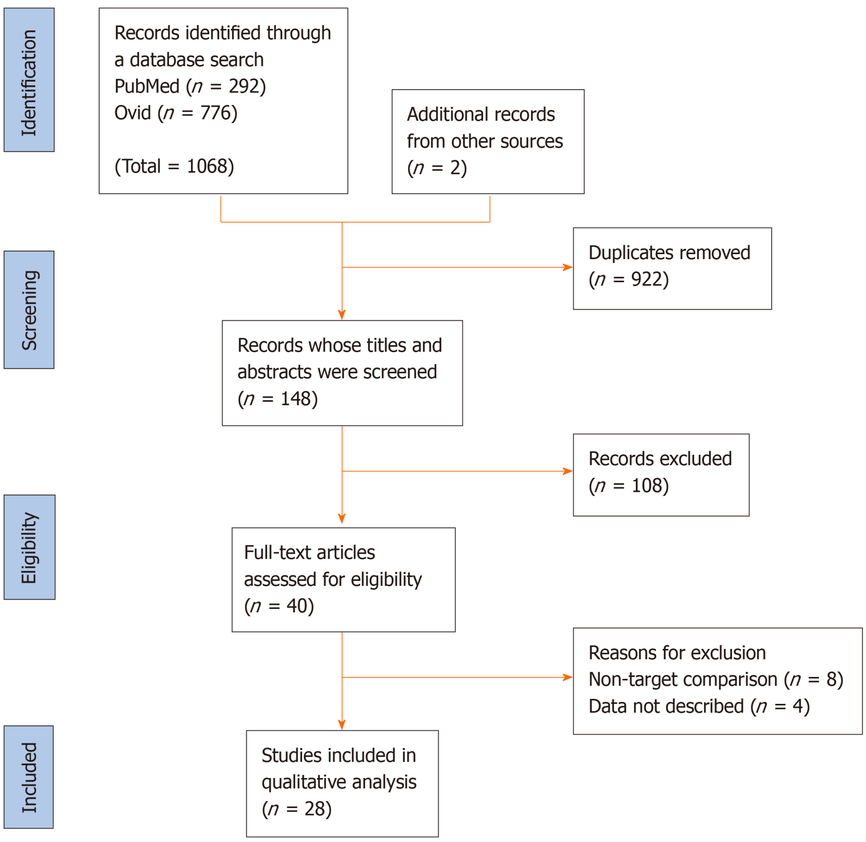

Figure 1 PRISMA flow diagram for this study.

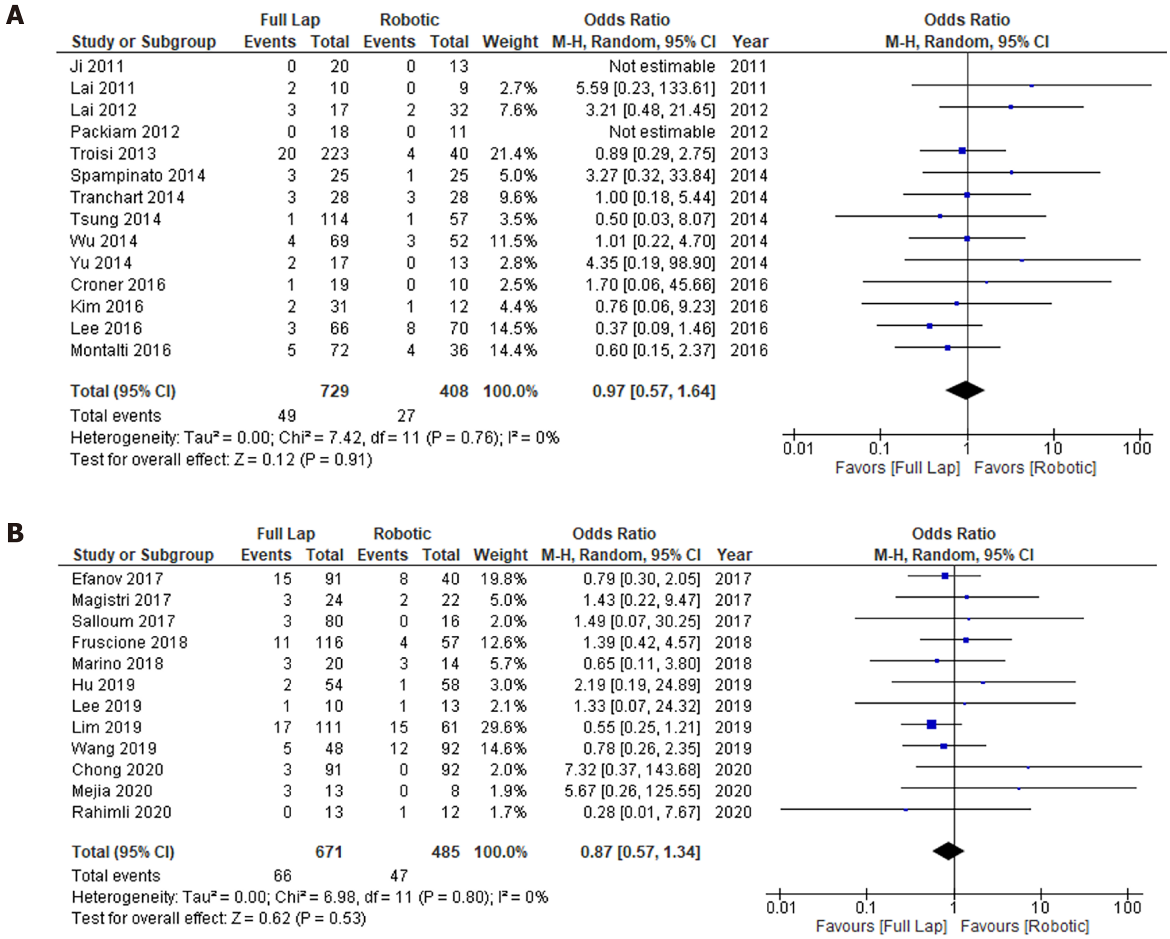

Figure 2 Frequency of Clavien-Dindo grade 3/4 complications. A: 2010-2016; B: 2017-2020.

tional studies. The types of liver resection performed did not differ significantly between the early (Table 1) and recent (Table 2) studies.

Frequency of Clavien-Dindo grade 3/4 complications

The data regarding complications of grade ≥ 3 according to the Clavien-Dindo (CD) classification are shown in Figure 2. There was no significant difference in the frequency of such complications between LLR and RLR in the early or recent studies. Scores of I^2 in both analyses were 0%, which indicated no heterogeneity. The funnel plots were shown in Supplementary Figure 1.

Intraoperative conversion rate

The data regarding the intraoperative conversion rate are shown in Figure 3. There was no significant difference in the intraoperative conversion rate between LLR and RLR in the early or recent studies. Score of I^2 in the early studies was 20% and the one in the recent studies was 44%. The heterogeneities were acceptable in the both analyses. The funnel plots were shown in Supplementary Figure 2.

Intraoperative blood loss

The data regarding intraoperative blood loss are shown in Figure 4. Although LLR tended to cause less intraoperative blood loss than RLR in the early studies, no marked difference in intraoperative blood loss between LLR and RLR was seen in the recent studies. Scores of I^2 in the early and recent studies were 88% and 94%, respectively. Severe heterogeneities were observed in both the early and recent analyses. The funnel plots were shown in Supplementary Figure 3.

Operation time

The data regarding the operation time are shown in Figure 5. Although in the early studies the operation time of LLR was significantly shorter than that of RLR (P < 0.0001), there was no significant difference between the operation times of LLR and

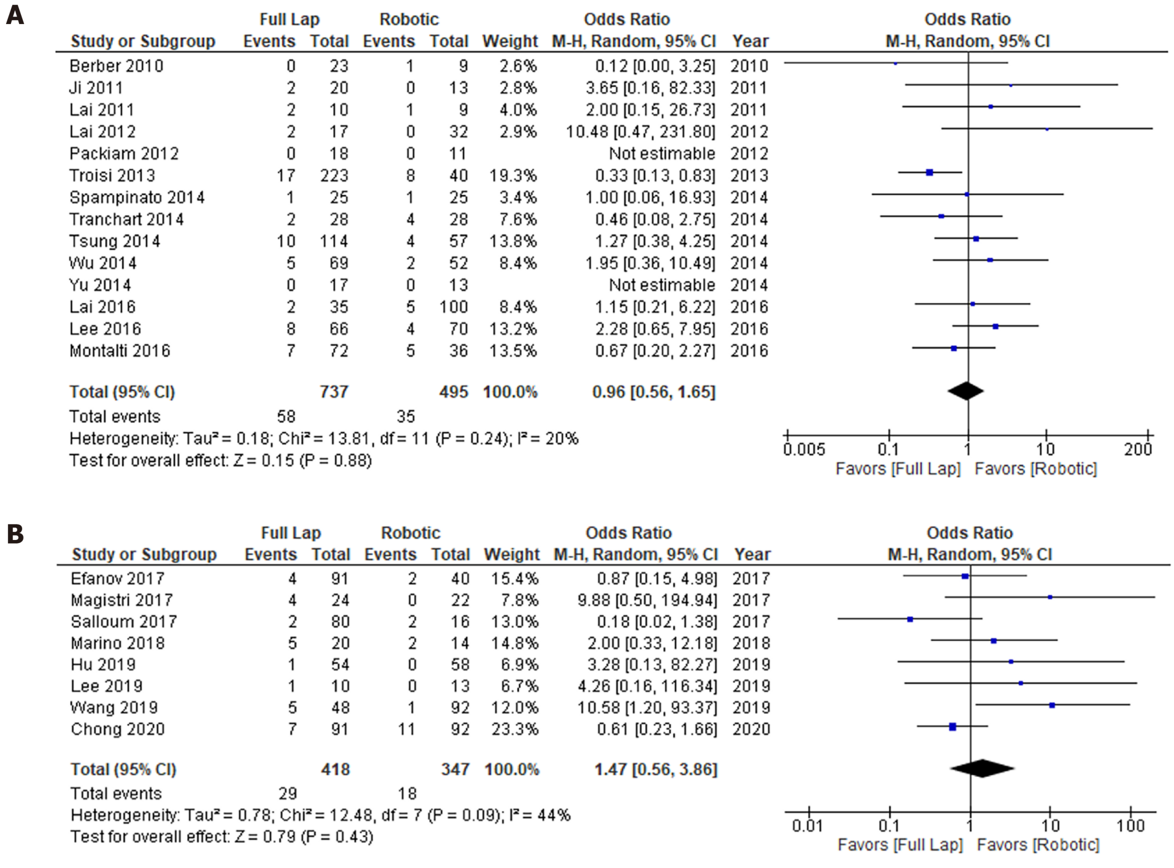

Figure 3 Intraoperative conversion rate. A: 2010-2016; B: 2017-2020.

RLR in the recent studies. Scores of I^2 in the early and recent studies were 81% and 93%, respectively. Severe heterogeneities were observed in both the early and recent analyses. The funnel plots were shown in Supplementary Figure 4.

Quality assessment of the bias

The quality assessment was conducted using the NOS score (Supplementary Table 1 and 2). There was no significant difference in the NOS score between the early and recent studies, although the quality of the studies varied. Summary of the publication bias in each analysis was shown in Supplementary Table 3.

DISCUSSION

MIS has become the standard approach for liver resection[1,4]. The initial disadvantages of RLR were that it involves large amounts of intraoperative blood loss and a long operation time. The recent studies examined in this review indicated that these initial disadvantages have been ameliorated. This finding strongly indicates that a new era of MIS may be upon us.

The CD classification is the standard grading system for surgical complications[43]. The definitions of the grades in the CD classification are based on how the complications are managed, *e.g.*, with pharmacological interventions, surgical interventions, or intensive care. These are indirect signs of complications. Furthermore, the grading system is divided into 5 grades plus 2 sub-grades. We did not find any difference in the types of complications encountered according to the CD classification between LLR/RLR or the early/recent period. This may have been because the CD classification is not suitable for identifying differences between clinical studies due to its use of indirect definitions and a relatively large number of grades. Ideally, surgical complications should be analyzed based on direct symptoms of the actual complications and a simple grading system[44].

LLR and RLR exhibited similar intraoperative conversion rates in both periods. The background data for each study varied, as they were all observational studies. The selection criteria for LLR and RLR were also unclear. Therefore, we could not conclude

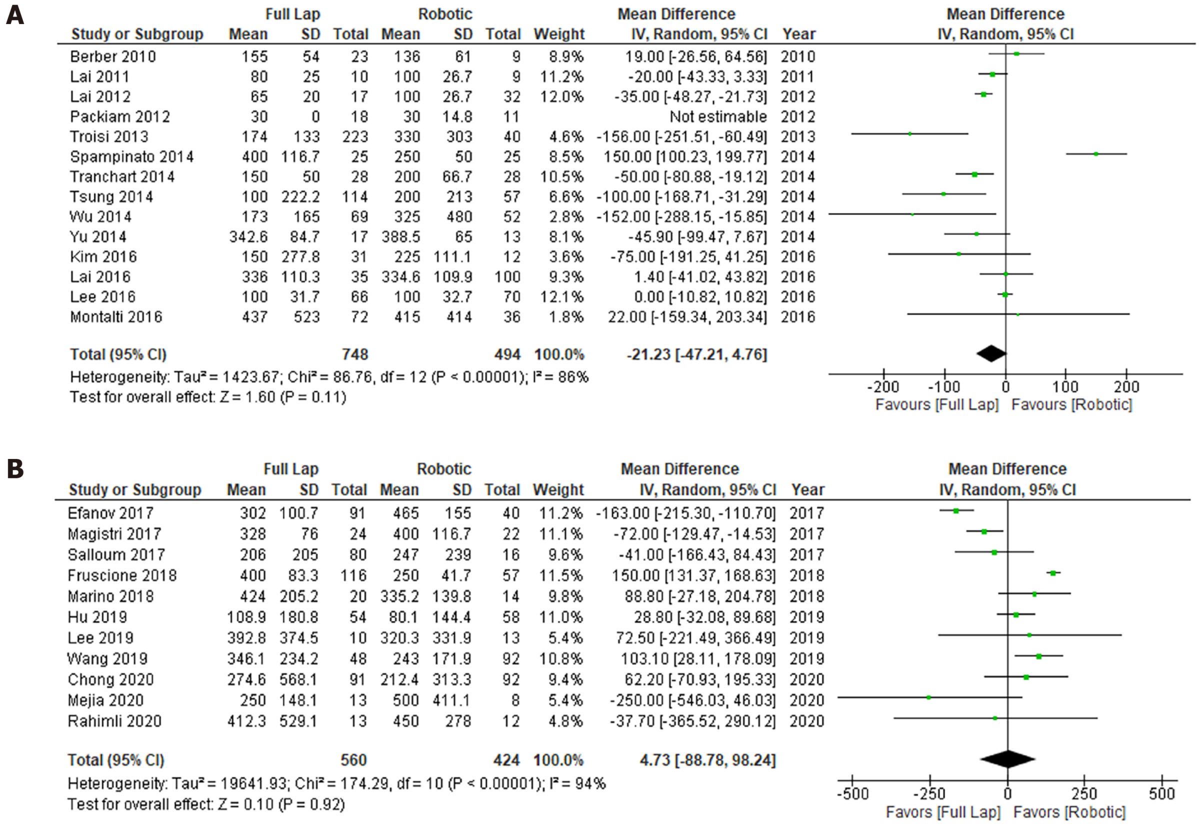

Figure 4 Intraoperative blood loss. A: 2010-2016; B: 2017-2020.

which type of surgery was safer. The maximum intraoperative conversion rate of LLR was about 25% among the recent studies. The maximum intraoperative conversion rate of RLR was about 20% among the early studies, although the mean conversion rate was < 10% in both study periods. In future, these rates could be used as standard clinical goals in order to ensure that surgical quality is maintained.

In the early studies, LLR tended to result in less intraoperative blood loss than RLR, although no marked differences in intraoperative blood loss were seen between LLR and RLR in the recent studies. Several strategies can reduce blood loss during pneumoperitoneum, such as using the head-up position, inducing a high peritoneal pressure, reducing the intratracheal pressure to increase the respiration time, reducing the respiratory volume, using a low central venous pressure, and employing inflow blood control based on the Pringle maneuver[2,45,46]. In addition, it is easier to change the body positions of patients during LLR than during RLR, which could help to control bleeding from veins. Various hemostatic devices are available, such as ultrasonic dissectors, and various hemostatic surgical devices were used for RLR in the recent studies, which may have counteracted the positional disadvantages of RLR. In addition to technical improvements associated with experience, various surgical devices can be used to reduce blood loss during RLR.

In the early studies, the operation time of the RLR was longer than that of the LLR. This is reasonable because it takes time to install robotic towers for robotic procedures. However, the difference in the operation time between the surgical procedures disappeared in the recent studies. It could be that the surgeons became familiar with the robotic procedures, which reduced the time required to set up the robot. Visual support and human-error-canceling functions could also have reduced the operation time[8]. Therefore, the initial disadvantages of RLR have recently been ameliorated.

One advantage of RLR is that it can be used to approach the dorsal segment and caudate lobe of the liver[47,48]. In addition, RLR is superior to LLR for bile duct reconstruction[49]. Therefore, separate tumor location- and surgical procedure-dependent indications need to be developed for RLR and LLR. The differences in the cost and quality-of-life outcomes of RLR and LLR should also be elucidated in the future.

This study had several limitations. First, all of the included studies were observational studies, and no RCT were identified. In addition, the indications for each procedure were not described clearly. The number of subjects recruited for each study

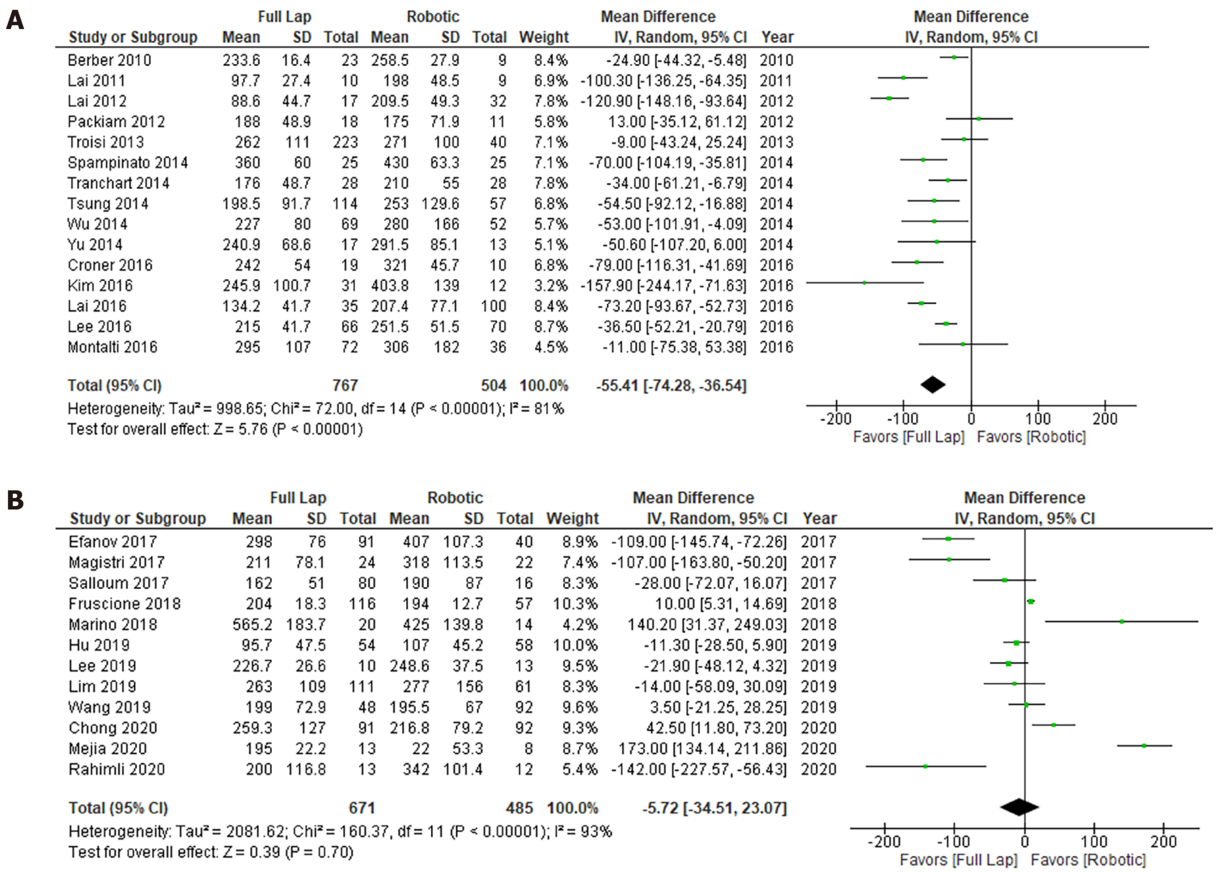

Figure 5 Operation time. A: 2010-2016; B: 2017-2020.

varied, as did the quality of each study. In addition, the clinical backgrounds of the studies differed. Although a few studies involved prospective protocols, at present there is no international registration system for such studies.

CONCLUSION

In conclusion, the initial disadvantages of RLR have been ameliorated. The clinical outcomes of LLR and RLR are comparable. Separate indications for each approach should be developed based on their cost and quality-of-life outcomes. A reliable international registration system for such cases needs to be established.

ARTICLE HIGHLIGHTS

Research background

Robotic liver resection (RLR) has emerged during the last decade. But the clinical outcome of the RLR has been debated.

Research motivation

Clinical outcomes among the laparoscopic liver resection (LLR) and RLR should be compared regarding merit and demerit.

Research objectives

The objective of this study was to conduct a systematic review and meta-analysis comparing the clinical outcomes of LLR and RLR over two 5-year periods.

Research methods

A systematic literature search was performed using PubMed and Medline, including the Cochrane Library.

Research results

A total of 25 articles were included in this meta-analysis after 40 articles had been subjected to full-text evaluations.

Research conclusions

The initial disadvantages of RLR, such as its long operation time, have been overcome during the last 5 years. The other clinical outcomes of RLR are comparable to those of LLR.

Research perspectives

The cost and quality-of-life outcomes of RLR should be evaluated in future studies to promote its routine clinical use.

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