—**Review**—

Surgical Site Infections in Gastroenterological Surgery

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Surgical site infections (SSIs) remain one of the most common serious surgical complications and are the second most frequent healthcare-associated infection. Patients with SSIs have a significantly increased postoperative length of hospital stay, hospital expenses, and mortality risk compared with patients without SSIs. The prevention of SSI requires the integration of a range of perioperative measures, and approximately 50% of SSIs are preventable through the implementation of evidence-based preventative strategies. Several international guidelines for SSI prevention are currently available worldwide. However, there is an urgent need for SSI prevention guidelines specific to Japan because of the differences in the healthcare systems of Japan versus western countries. In 2018, the Japan Society for Surgical Infection published SSI prevention guidelines for gastroenterological surgery. Although evidence-based SSI prevention guidelines are now available, it is important to consider the appropriateness of these guidelines depending on the actual conditions in each facility. A systemic inflammatory host response is a hallmark of bacterial infection, including SSI. Therefore, blood inflammatory markers are potentially useful in SSI diagnosis, outcome prediction, and termination of therapeutic intervention. In this review, we describe the current guideline-based perioperative management strategies for SSI prevention, focusing on gastroenterological surgery and the supplemental utility of blood inflammatory markers.
(J Nippon Med Sch 2023; 90: 2–10)

Key words: surgical site infection, gastroenterological surgery, prophylactic antibiotics, blood inflammatory marker

Introduction

Surgical care is an integral part of healthcare, with an estimated 313 million surgical procedures performed worldwide annually. Surgical care is associated with a considerable risk of complications and death. It is estimated that 42 million people worldwide die within 30 days of surgery every year, accounting for 7.7% of all deaths globally and making surgery the third greatest cause of death after ischemic heart disease and stroke[1].

Surgical site infections (SSIs) remain one of the most common serious surgical complications. Although the incidence of SSI is lower in high-income countries, SSIs affect up to one-third of patients who have undergone a surgical procedure in low- and middle-income countries. Furthermore, SSIs are still the second most frequent healthcare-associated infection in Europe and the United States[2]. In the United States, recent data show that SSI accounts for over two million nosocomial infections in patients who have been hospitalized[3]. SSIs significantly increase the postoperative length of hospital stay by approximately 7-10 days, increase the hospital expenses, and carry a 2-11-fold higher risk of death compared with patients without SSIs, regardless of improved surgical practice, surveillance, and infection-control techniques[4–6]. Importantly, it is estimated that approximately 50% of SSIs are preventable through the implementation of evidence-based preventative strategies[7]. The present review focuses on the pathophysiology, prevention, and prediction of SSIs in gastroenterological surgeries.

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https://doi.org/10.1272/jnms.JNMS.2023_90-102
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Table 1 Recently published or updated guidelines for prevention of surgical site infection

Year of publication	Publisher	Guideline	Timing of prophylactic ABS	Re-dosing of prophylactic ABS	Postoperative prophylactic ABS	Targeted blood glucose level
2019	National Institute for Health and Care Excellence (NICE)	Surgical site infection: prevention and treatment	before starting anesthesia	recommended	not recommended	Do not give insulin routinely to optimize blood glucose
2018	Japan Society for Surgical Infection (JSSI)	Gastroenterological Surgery, guideline of perioperative management for the prevention of surgical site infection	within 60 min before incision	no recommendation	gastric surgery: not recommended, colon surgery: efficacy is unknown	≤150 mg/dL
2017	Centers for Disease Control and Prevention (CDC)	Guideline for the prevention of surgical site infection, 2017	before the incision	no recommendation	not recommended	≤200 mg/dL
2016	American College of Surgeons/Surgical Infection Society (ACS/SIS)	Surgical site infection guidelines, 2016 update	within 60 min before incision	recommended	not recommended	110-150 mg/dL
2016	World Health Organization (WHO)	Global guidelines for the prevention of surgical site infection	within 120 min before incision	no recommendation	not recommended	110-150 mg/dL
2016	Japanese Society of Chemotherapy/Japan Society for Surgical Infection (JSC/JSSI)	Practical Guidelines for the Appropriate Use of Antimicrobial Agents for Postoperative Infection Prevention	within 60 min before incision	every 3-4 hours	Intraoperative ～ until 24 hrs	not mentioned

ABS: antibiotics

Guidelines for the Prevention of Surgical Site Infection

Recently published or updated guidelines for SSI prevention are listed in **Table 1**. In 2017, the Centers for Disease Control and Prevention (CDC) published updated Guidelines for the Prevention of Surgical Site Infection for the first time in 18 years[8]. These guidelines focus on selected areas of SSI prevention with sufficient evidence, and comprise recommendation and commentary parts. The recommendation part includes six core sections regarding SSI prevention in all surgical procedures, and seven that relate specifically to prosthetic joint arthroplasty. The six general core sections are parenteral antimicrobial prophylaxis, nonparenteral antimicrobial prophylaxis, glycemic control, normothermia, oxygenation, and antiseptic prophylaxis. These guidelines continue to recommend parts of the 1999 guidelines[9], and reiterate the recommendations in supplement eAppendix 1.5. However, the 2017 Guidelines for the Prevention of Surgical Site Infection only contain general comments, without providing details on SSI prevention techniques that should be implemented in clinical practice.

In 2016, the World Health Organization (WHO) published the "Global guidelines for the prevention of surgical site infection"[10]. Because SSIs are epidemiologically important and largely preventable, the WHO prioritized the development of evidence-based recommendations for SSI prevention. One of the major characteristics of the WHO guidelines is the assumption that they will be used in low- and middle-income countries.

The Japan Society for Surgical Infection (JSSI) published the "Guidelines for the prevention, detection, and management of gastroenterological surgical site infection" in 2018[11]. Considering the differences between Japan and western countries regarding healthcare insurance and equipment, race, physique, and surgical procedures, there was an urgent need for Japan-specific guidelines. The JSSI guidelines are internationally unique because they focus on gastroenterological surgery and suit the

Japanese medical system in which surgeons treat patients throughout the perioperative period. The evidence-based JSSI guidelines use the Grading of Recommendations, Assessment, Development and Evaluation system[12] that are also adopted in the CDC[8] and WHO[10] guidelines, are based on studies published from 2000 onwards, and are suited for clinical practice in Japan targeting all medical staff involved in SSI prevention in gastroenterological surgery.

Definition and Epidemiology of Surgical Site Infection

Perioperative infection is broadly classified into surgical field infection (i.e., SSI) and remote infection (RI). SSIs are classified as superficial incisional, deep incisional, and organ/space SSIs that occur within 30 or 90 days after surgery, depending on the surgical procedure[8]. RI is defined as perioperative infection that occurs in areas not directly subjected to surgical manipulation, and includes infections such as pneumonia, antimicrobial-associated enteritis, urinary tract infection, and catheter-related blood stream infection. The main cause of SSIs is intraoperative contamination with bacteria, including intestinal flora and resident skin flora. In contrast, most RIs are caused by cross-infection with bacterial contaminants in the hospital environment through the hands of medical staff[13].

The incidence of SSIs is higher in gastroenterological surgery than other surgeries, and gastroenterological SSIs account for over 80% of all SSIs. Japanese nationwide surveillance data (204,763 cases of gastroenterological surgery) demonstrated that the incidences of overall SSIs, superficial, deep incisional, and organ/space SSIs in 2019 were 7.7%, 3.5%, 0.7%, and 3.6%, respectively. The incidences of SSIs in colon surgery, rectal surgery, esophageal surgery, and panreaticoduodenectomy were 9.3%, 12.2%, 17.5%, and 25.5%, respectively, and are decreasing annually[14]. The European Centre for Disease Prevention and Control reported that the incidences of SSI in laparoscopic and open colon surgeries in 2017 were 6.4% and 10.1%, respectively[15]; the incidences of SSIs in both procedures are reportedly decreasing, which is consistent with the trends in Japan.

Perioperative Management for the Prevention of Surgical Site Infection

Prophylactic Antimicrobial Therapy

The purpose of prophylactic antimicrobial therapy is to reduce the sensitive bacterial load and enhance the antibacterial function of immunocompetent cells (e.g., phagocytosis by neutrophils), resulting in the reduction of SSIs. However, prophylactic antibiotics have no reported preventative effect for RIs. Therefore, clinicians should select drugs with antimicrobial activity against the indigenous bacterial flora of the surgical site rather than drugs targeting bacteria that cause postoperative infection. Furthermore, drug selection must take into account potential adverse effects, induction of resistant bacteria, and medical cost[9,16]. The WHO[10], American College of Surgeons an Surgical Infection Society (ACS/SIS)[17], and National Institute for Health and Care Excellence (NICE)[18] guidelines recommend prophylactic antimicrobial therapy comprehensively, without distinguishing between surgical procedures, while the Guidelines for the Appropriate Use of Antimicrobial Agents in Japan by the Japanese Society of Chemotherapy (JSC)/JSSI describe recommendations for each surgical technique[19].

Adequate tissue concentrations of prophylactic antibiotics should be present at the time of incision and throughout the surgical procedure. However, the optimal timing of prophylactic antibiotic administration is debatable. A meta-analysis showed that the incidence of SSIs is higher in patients administered prophylactic antibiotics more than 120 minutes before the incision than in those administered antibiotics within 120 minutes before the incision; the incidence of SSI did not significantly differ between groups administered antibiotics at 60-120 minutes vs. 0-60 minutes before the incision, or between groups administered antibiotics at 30-60 minutes vs. 0-30 minutes before the incision. Based on these data, the WHO guidelines recommend prophylactic antibiotic administration within 120 minutes before the incision[10]. Other guidelines recommend prophylactic antibiotic administration 60 minutes before the incision, including the ACS/SIS guidelines[17] and JSSI guidelines[11] (**Table 1**).

Intraoperative re-dosing of prophylactic antibiotics may be necessary in longer surgeries to maintain therapeutic levels, as recommended in the 1999 CDC guidelines[9]. The timing of repeat doses of antibiotics is based on the drug half-life, as each drug should be readministered at approximately every 1.5 times the half-life[8]. Only one randomized controlled trial (RCT) published in 1991 has compared the use of single- and double-dose antibiotics in colorectal surgery, with re-dosing failing to show a reduction in the incidence of SSI[20]. Although other retrospective studies have suggested a beneficial effect of re-dosing in various surgeries[21,22], the efficacy of re-dosing remains unclarified. While re-dosing seems to have benefits from a pharmacokinetic aspect, there are no recommendations for re-dosing in the guidelines of the CDC[8], WHO[10], and JSSI[11] (**Table 1**). Furthermore, the therapeutic level of antibiotics may theoretically be affected by conditions such as excessive intraoperative blood loss. The ACS/SIS guidelines recommend re-dosing every 1,500 mL of blood loss[17]. However, due to a lack of evidence, the CDC[8], WHO[10], and JSSI[11] guidelines do not provide clear recommendations regarding re-dosing in patients with excessive blood loss or obesity.

The approaches for postoperative prophylactic antibiotics differ between Japan and western countries. The CDC[8] and WHO[10] guidelines do not recommend postoperative prophylactic antibiotics because of the unclear efficacy and the risks of the selection and emergence of resistant strains and *Clostridium difficile* infection; however, these guidelines do not give separate recommendations for each surgical procedure. Historically, postoperative prophylactic antibiotics have been used for a long time in Japan. The JSSI guidelines[11] are based on meta-analyses of gastric and colorectal cancer surgeries that compared intraoperative administration (and intraoperative re-dosing) versus extension to the postoperative period. The JSSI guidelines recommend only intraoperative prophylactic antibiotics in gastric cancer surgery based on the meta-analysis of four RCTs[23–26]. As only two RCTs have evaluated prophylactic antibiotic administration in colorectal cancer surgeries[27,28], the JSSI guidelines do not make specific recommendations regarding the dosing period of prophylactic antibiotics in colon surgery (**Table 1**). However, most surgeries in the assessed studies were performed via laparotomy. Because laparoscopic surgery is now the gold standard and contributes to a reduction in the incidence of SSI[29,30], further studies are warranted to evaluate the non-inferiority of intraoperative prophylactic antibiotics compared with the extension to the postoperative period in the era of laparoscopic surgery.

Blood Glucose Control and Preoperative Carbohydrate Loading

Surgery causes a stress response that releases catabolic hormones, inhibits insulin production, and induces insulin resistance[31]. This relative hypoinsulinemia followed by hyperglycemia is associated with an increase in SSIs, even in non-diabetic patients[32,33]. While the importance of blood glucose control in preventing SSIs is widely established, the optimal target blood glucose levels remain controversial. Previous studies targeting low perioperative glucose levels under intensive control showed a favorable reduction in the occurrence of SSIs, but highlighted the adverse effects of hypoglycemia[34,35]. Therefore, most guidelines recommend glucose levels of 150-200 mg/dL. The 2017 CDC guidelines recommend the implementation of perioperative glycemic control, with target blood glucose levels of less than 200 mg/dL in both diabetic and non-diabetic patients[8]. The WHO guidelines recommend intensive glucose control for both diabetic and non-diabetic surgical patients, with target glucose levels of 110-150 mg/dL or less than 150 mg/dL[10]. The JSSI guidelines state that target glucose levels of 80-110 mg/dL are preferred in terms of SSI prevention, but recommend levels of less than 150 mg/dL considering the risk of hypoglycemia[11]. The optimal duration and frequency of glucose measurement are undetermined. If intensive glycemic control is performed, the protocol should be modified in accordance with the actual situation at each facility.

The 'enhanced recovery after surgery' program is a patient-centered, evidence-based, multidisciplinary team-developed comprehensive protocol to reduce the surgical stress response, optimize the physiologic function, and facilitate postoperative recovery[36]. One of the elements of the 'enhanced recovery after surgery' program is preoperative carbohydrate loading, which reportedly suppresses insulin resistance and controls postoperative hyperglycemia (i.e., maintains normoglycemia)[37,38]. Furthermore, carbohydrate loading alleviates symptoms of discomfort, such as mouth dryness, thirst, and hunger, without safety concerns[39]. Theoretically, carbohydrate loading was expected to reduce SSIs through the effect of glycemic control, but clinical trials failed to show improvements in survival and postoperative infections[40,41].

Perioperative Nutritional Support

Nutritional status greatly impacts the immune system, and malnutrition in surgical patients contributes to delayed recovery and high susceptibility to postoperative infection, followed by prolonged hospitalization and increased medical costs[42]. The recent increase in sarcopenic and/or frail surgical patients due to the aging population is reportedly causing increased rates of postoperative morbidity and mortality. Therefore, the importance of nutritional support is increasingly being recognized[43,44]. Meta-analyses have clearly demonstrated increased occurrences of SSIs, while preoperative nutritional modulation reduced the incidence of SSIs in malnourished surgical patients based on the JSSI guidelines[11]; however, immune-enhancing nutritional modulation did not reduce the incidence of SSI in surgical patients without malnutrition. The WHO guidelines also recommend the administration of oral or enteral multiple nutrient-

Table 2 Definitions of patients with malnutrition

ESPEN	GLIM				
	Phenotypic criteria			Etiologic criteria	
	Weight loss (%)	Low BMI	Reduced muscle mass	Reduced food intake or assimilation	Inflammation
Presence of at least one of following criteria: ・Weight loss >10-15% within 6 months ・BMI <18.5 kg/m^2 ・SGA Grade C or NRS >5 ・Preoperative serum albumin 30 g/L (with no evidence of hepatic or renal dysfunction)	>5% within past 6 months or 10% beyond 6 months	<20 if <70 years, or <22 if >70 years Asia: <18.5 if <70 years or <20 if >70 years	Reduced by validated body composition measuring techniques	≤50% of ER >1 week or any reduction for >2 weeks or any chronic GI condition that adversely impacts food assimilation or absorption	Acute disease/injury or chronic disease-related

ESPEN: The guideline of the European Society for Clinical Nutrition and Metabolism in 2017 [45], BMI: Body mass index, NRS: Nutritional risk screening, GLIM: The definition of the Global Leadership Initiative on Malnutrition [46], ER: energy requirements, GI: gastrointestinal

Table 3 Reported risk factors for surgical site infection

Patient-related	Procedure-related
age	surgical hand preparation
gender	surgical site preparation
nutritional status	hair removal
diabetes	duration of surgery
steroid use	blood transfusion
smoking	surgical procedure
severe obesity	colostomy
preoperative length of hospital stay	emergency surgery
ASA score	antimicrobial-coated suture
dirty wound	
preoperative chemoradiotherapy	

ASA: American Society of Anesthesiologists

enhanced nutritional formulas to prevent SSIs in underweight patients scheduled for major surgery[10]. However, there are no established criteria for diagnosing malnutrition in surgical patients. The 2017 guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN)[45] define the diagnostic criteria for malnutrition as 1) weight loss > 10%-15% within 6 months, 2) body mass index (BMI) < 18.5 kg/m^2, 3) subjective global assessment grade C or nutritional risk screening score > 5, and 4) preoperative serum albumin < 30 g/L (with no evidence of hepatic or renal dysfunction). The ESPEN guidelines recommend a nutritional assessment more than 2 weeks before surgery, and nutritional intervention for 7-10 days for malnourished patients. In 2018, four academic societies in Europe, the United States, Asia, and South America participated in the formulation of the first international standard for diagnosing malnutrition. The Global Leadership Initiative on Malnutrition (GLIM) defines malnutrition based on phenotype (weight loss, low BMI, reduced muscle mass) and cause (reduced food intake, inflammation)[46] (**Table 2**); this definition involves not only reduced food intake, but disease-related malnutrition, which is a recently established concept and is closely linked to inflammation. Recent studies have demonstrated that the criteria perform well in the nutritional assessment and survival prediction of patients with various types of cancer[47]. Large-scale clinical trials are warranted to evaluate the effect of nutritional intervention based on these criteria in preventing SSI.

Risk Factors for Surgical Site Infection in Gastroenterological Surgery

The risks of delayed wound healing and SSI occurrence are increased by patient-related factors (age, sex, smoking status, nutritional status) and procedure-related factors (surgical hand preparation, surgical site preparation, hair removal, prophylactic antimicrobial therapy, antimicrobial-coated sutures) (**Table 3**). The uncontrollable factors, such as age, sex, and surgical procedure, should be adjusted for in interinstitutional comparisons of SSI occurrence rates.

A study of patient-related risk factors for SSI after eight categories of gastrointestinal surgery based on the Japan Nosocomial Infections Surveillance program found that intraoperative blood transfusion was a risk factor for SSI in all surgeries, except appendectomy and small bowel surgery[48]; diabetes and steroid use were risk factors in certain surgeries (gastric and colon surgery for diabetes; cholecystectomy and colon surgery for steroid use). A recent study found that the risk factors for SSI in laparoscopic colorectal cancer surgeries performed in a high-volume cancer center in Japan were abdominoperineal resection, BMI more than 25 kg/m^2, and preoperative chemoradiotherapy, while no significant risk factors were identified in laparoscopic colon surgeries[49]. In the Japan Nosocomial Infections Surveillance database, gastric surgeries are divided into three types of procedures: total gastrectomy, distal gastrectomy, and other types of gastric surgery. Although the effect on SSI development is different for each type of gastric procedure, male sex and emergency surgery are risk factors for SSI in all types of gastric surgery[50]. The JSSI guidelines[11] state that the risk factors for SSI in gastroenterological surgery are an American Society of Anesthesiologists score of more than 3, surgical wound classification of more than 3, prolonged operation time, diabetes, severe obesity, malnutrition, current smoking status, and intraoperative blood transfusion based on a meta-analysis of seven retrospective studies[48,51–56]. It is necessary to prioritize the risk factors by the strength of their effect on SSI development and work toward eliminating SSIs through further prospective interventional studies based on risk assessment.

Systemic Inflammatory Responses in Surgical Site Infection

The physiologic derangements induced by bacterial infection are due to the host responses to the invading microorganisms as opposed to the direct effects of the microorganism itself. Bacterial infections (including SSIs) are characterized by systemic inflammatory responses mediated by immunocompetent cells, such as the production of inflammatory cytokines and various mediators[57,58]. Therefore, assessments of these inflammatory markers have considerable potential in auxiliary diagnosis, prediction of the occurrence and outcome, and termination of therapeutic intervention in the clinical course of SSIs.

Interleukin-(IL) 6, a representative inflammatory cytokine, and C-reactive protein (CRP), an acute phase protein, during the perioperative period might usefully identify patients at risk of SSIs. A recent study associated high IL-6 levels on postoperative day 1 with an increased risk of complications after major abdominal surgery, but its predictive value is not so high (area under the curve: 0.67)[59]. Several studies demonstrated that CRP measurements on postoperative day 3 (or 4) are useful in predicting SSIs, especially for anastomotic leakage, with optimal predictive threshold values from 125 mg/L to 190 mg/L in CRC surgeries[60–62].

Lysophosphatidylcholine (LPC) is a lipid mediator derived from membrane phospholipids that has been suggested to have immunosuppressive potential and regulate the excessive immune response. Patients with sepsis reportedly have significantly decreased blood levels of LPC, and the LPC level has good efficacy in predicting the outcome of bacterial sepsis[63,64]. Serial perioperative measurements of blood LPC levels using a quick enzymatic assay in highly invasive (esophageal or hepatobiliary pancreatic surgery), medium-level invasive (colorectal surgery), and minimally invasive surgeries (laparoscopic cholecystectomy) demonstrated significant LPC decreases after surgery in all groups, with the decrease dependent on the degree of surgical invasiveness. There was a marked early postoperative decrease in the LPC level in patients with postoperative complications (mainly SSIs), and this decreased LPC level was an independent risk factor for SSI in colorectal cancer surgery (**Fig. 1**)[65].

Procalcitonin (PCT) is a representative inflammatory marker produced by parenchymal organs in association with bacterial infection. Studies have clarified the efficacy of blood PCT measurements in the prediction of SSIs in various gerontological surgeries[66–68]. In addition, PCT is the most commonly evaluated inflammatory marker, making it potentially useful as an indicator of the suitability of shortening the duration of antimicrobial therapy in critically ill septic patients[69,70]. Furthermore, a recent meta-analysis showed the survival benefit of a PCT-based algorithm in ICU patients with infection and sepsis[71]. A prospective propensity score-matched study reported that a PCT-based algorithm safely reduced the duration of antibiotic exposure from 6.1 days in the control group to 3.4 days in patients with secondary peritonitis following emergency surgery[72]. However, the effectiveness of a PCT-guided algorithm as an antibiotic discontinuation strategy in patients with SSI after gastroenterological surgery is undetermined and should be investigated in future trials.

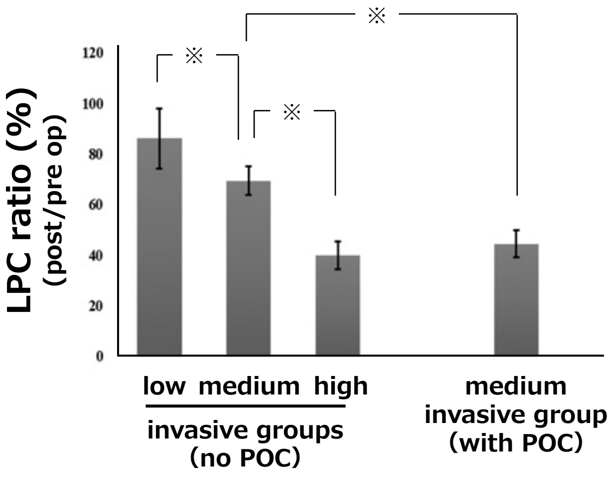

Fig. 1 The association between blood lysophosphatidylcholine ratio and postoperative complications
Patients were divided into high-invasive (esophageal or hepatobiliary pancreatic surgery), medium-invasive (colorectal surgery) and low-invasive (laparoscopic cholecystectomy).
LPC: lysophosphatidylcholine, Values are expressed as mean ± Standard error, POC: postoperative complications, ※*P*<0.05

Conclusion

This review described the current guideline-based perioperative management for SSI prevention in gastroenterological surgery. Although these guidelines are evidence-based, each of the recommendations are not always consistent in a single clinical situation. Each institution should critically examine the recommendations of each of the guidelines and decide whether to adopt them.

Acknowledgement: We thank Kelly Zammit, BVSc, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Funding: No funding was received for this study.

Conflict of Interest: Authors declare no Conflicts of Interest for this article.

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(Received, February 15, 2022)
(Accepted, April 13, 2022)
(J-STAGE Advance Publication, May 30, 2022)