ERCP SUCCESS RATE AND PERIAMPULLARY DIVERTICULA

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Abstract

The periampullary diverticulum (PAD) is an outpouching herniation in the duodenal wall near the major duodenal papilla. It refers to a mucosal or submucosal outpouching of duodenum and they are frequently found in the second part of the duodenum adjacent to the ampulla, commonly caused by a defect of the local muscular layer and arising within a 2~3 cm radius of the major papilla. The duodenum, second to the colon, is the most frequent site for gastrointestinal diverticulum. Endoscopic retrograde cholangiopancreatography (ERCP), one of the more challenging procedures performed by gastroenterologists, is associated with higher rates of complications than general endoscopy. higher-volume centers with more experienced practitioners have superior outcomes with lower adverse events than do lower-volume centers. The variation in location of the papilla in the setting of PAD can lead to an atypical orientation or obscured location, complicating endoscopic cannulation and stone extraction using traditional techniques. Indeed, there are many case reports highlighting innovative techniques to facilitate biliary cannulation in the setting of PAD including clip placement, the use of small diameter forceps, cap-fitted forward viewing endoscopy, and a reverse guide wire technique. Successful ERCP includes not just cannulation but also completion of therapy, often including stone extraction. Large stone removal can be difficult in the setting of PAD, when the altered anatomy and concern for perforation may limit the sphincterotomy length. The literature also supports a reduced rate of successful stone removal in patients with PAD with endoscopic sphincterotomy alone. It is reasonable to estimate that this may have contributed to the less successful ERCPs in earlier studies, when balloon sphincteroplasty, endoscopic hydraulic lithotripsy, and other techniques for stone extraction may not have been as widely available. A recent multicenter retrospective review stressed the considerable efficacy of balloon dilation in the extraction of large CBD stones in setting of PAD.

Keywords: ERCP, periampullary diverticula

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The periampullary diverticulum (PAD) is an outpouching herniation in the duodenal wall near the major duodenal papilla **(1)**.

It refers to a mucosal or submucosal outpouching of duodenum and they are frequently found in the second part of the duodenum adjacent to the ampulla, commonly caused by a defect of the local muscular layer and arising within a 2~3 cm radius of the major papilla. The duodenum, second to the colon, is the most frequent site for gastrointestinal diverticulum. **(2)**.

It is the most common anomaly that causes difficulty with the cannulation of the common bile duct or pancreatic duct. At endoscopy, identification of the papilla is the first major obstacle, especially in the presence of large diverticula. In these cases, it is extremely helpful to know that in the vast majority of cases, the papilla is located on the lower rim of the diverticulum or just inside, somewhere between 4 and 8 o'clock. In less than 5% of cases, it may be buried within the diverticulum and access may be difficult **(2)**

Based on the involvement of the ampulla by these lesions, they are divided into 3 separate subtypes Type (I): ampullary diverticula if the papilla is found inside the diverticula and Type (II): juxta ampullary or juxta papillary if the papilla is not involved(outside the papilla) or Type (III): located on the edge of the papilla **(3).**

These lesions are usually acquired by the progression of duodenal motility disorders and may arise from traction of the bile duct on the duodenal wall. A congenital factor may play a role as the duodenum has some weak spots with defects in musculature arising from abortive attempts to form supernumerary pancreas **(4)**.

Statistically, periampullary diverticula are rare in patients below 40 years it's usually found in the elderly, slightly more frequently in females than in males **(1)**.

Most of these herniations are composed of cystic lesions that acquired during life, with a higher prevalence in individuals 50 to 60 years old more than 75.5%.

Periampullary diverticulum is usually asymptomatic and diagnosed incidentally as reported in 2–5% of patients undergoing barium studies of the upper gastrointestinal tract and in 7% of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) and only 5% of these patients develop complications such as bleeding, perforation, and pancreatitis. Generally, the association of PAD with pancreatitis, biliary obstruction, choledocholithiasis and rarely cancer has been called Lemmel's syndrome or juxtapapillary syndrome **(5)**.

Choledocholithiasis is a common disease of the biliary tract system, and its causes are not completely clear, but its occurrence is closely related to periampullary diverticulum (PAD). It was reported that the incidence of bile duct stones reached 51.3%-88.0% among PAD patients **(5)**

Lemmel's syndrome was first described in 1934 by Lemmel as an obstructive jaundice caused by a periampullary duodenal diverticulum compressing the intra-pancreatic part of the common bile duct with resultant upstream dilatation of the extra- and intra-hepatic bile ducts. **(6)**

Given the range of clinical presentations, the diagnosis of Lemmel's syndrome is most reliably made by imaging associated with abnormal cholestatic patterns on serum chemistries, including an elevated bilirubin and liver enzymes may strengthen the diagnosis, but they may also be normal despite radiographic evidence of biliary dilatation. **(7)**

Interestingly, while abdominal ultrasonography has been commonly utilized in the initial diagnostic work-up in past reports, the diagnosis of Lemmel's syndrome has never been made based on ultrasonography alone, and additional imaging has always been required, CT abdomen and pelvis with contrast appears to be a sensitive test and is most commonly performed in cases of suspected Lemmel's syndrome appearing as an out pouching of the intestinal wall containing air, an air-fluid level, or debris. **(8)**

Unfortunately, abdominal CT exams lack specificity, and a duodenal diverticulum may be falsely interpreted as a possible pancreatic neoplasm or pseudocyst **(8)**

Thus, a suspected case of Lemmel's syndrome seen on CT scan may require a more definitive study such as MRCP or endoscopy while examination with a side-viewing duodenoscope allows better visualization of periampullary duodenal diverticula and for immediate endoscopic intervention. For these reasons, ERCP has been heralded as the gold standard in previous studies **(9)**

However, it appears that the diagnosis of Lemmel's syndrome is made only approximately 50% at the time of endoscopy, and the diagnosis can and has been made by MRCP and other radiographic modalities alone **(10)**

The diagnosis can also be made surgically with direct visualization of the periampullary diverticulum, but this is the last option given its invasiveness and non-inferiority to the other alternatives **(11)**

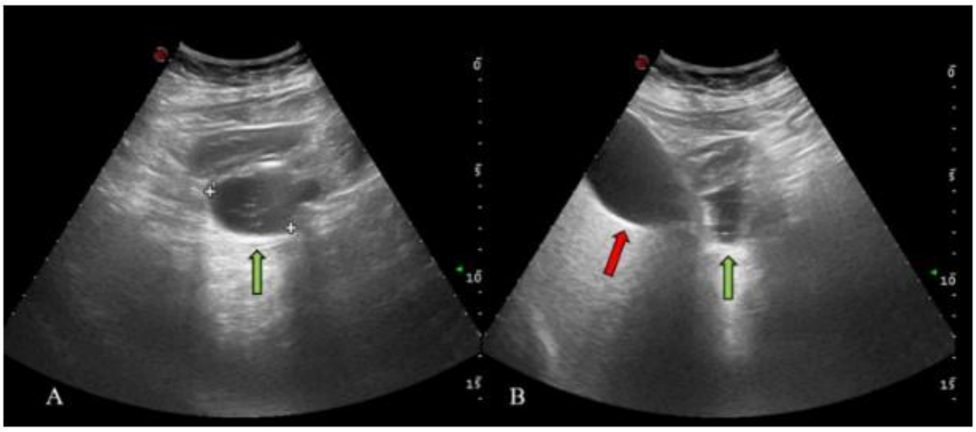

Figure (1): Abdominal US showing hypo-anechoic, rounded, 4 cm mass (green arrow) with multiple hyperechoic spots inside; gallbladder on the right of the PAD (red arrow) to be confirmed by another imaging modality **(9)**

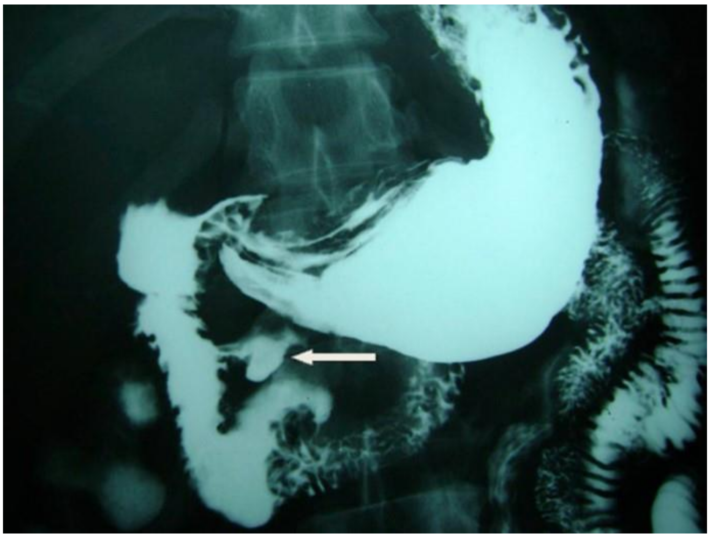

Figure (2): barium study showing periampullary diverticula as contrast-filled outpouchings arising from the medial side of the descending duodenum **(12)**

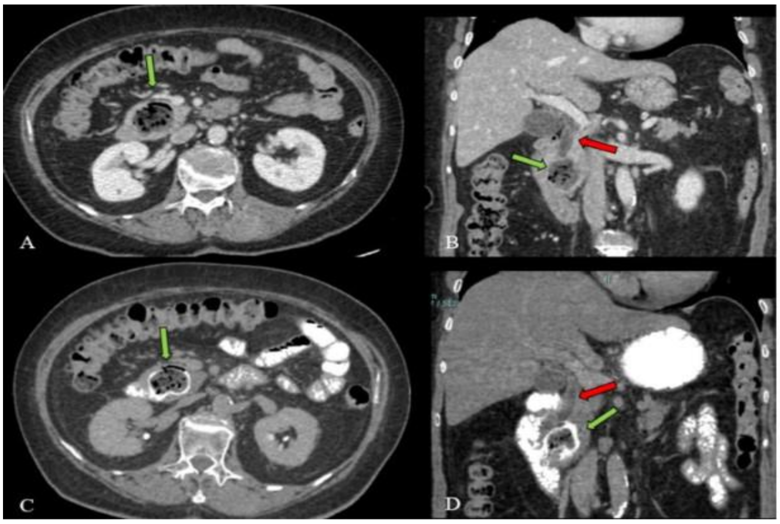

Figure (3): NECT (A-B) and CECT with oral contrast administration (C-D). 4 cm PAD filled by food (green arrow). Oral contrast (C-D) was administrated to better identify diverticulum. Coronal reconstructions (B-D) show the bile duct dilatation (red arrow) due to extrinsic compression of PAD (green arrow) **(9)**

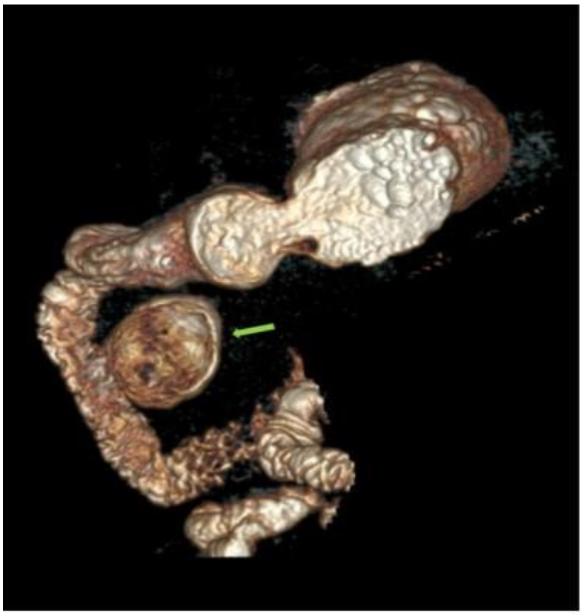

Figure (4): Three-dimensional CT reconstruction with volume rendering (3D-VR), after oral contrast administration, shows PAD (green arrow) **(9)**

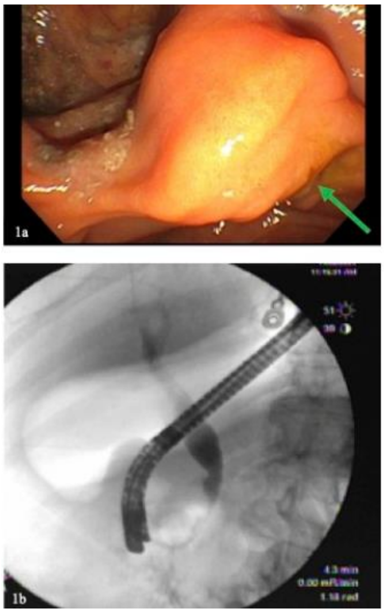

Figure (5): (1a) Periampullary diverticulum, with solid arrow demarcating the papilla and dashed arrow revealing the large periampullary diverticulum containing smaller internal diverticuli. (1b) ERCP with cholangiogram showing external compression of CBD by the periampullary diverticulum with upstream ductal dilation **(13)**

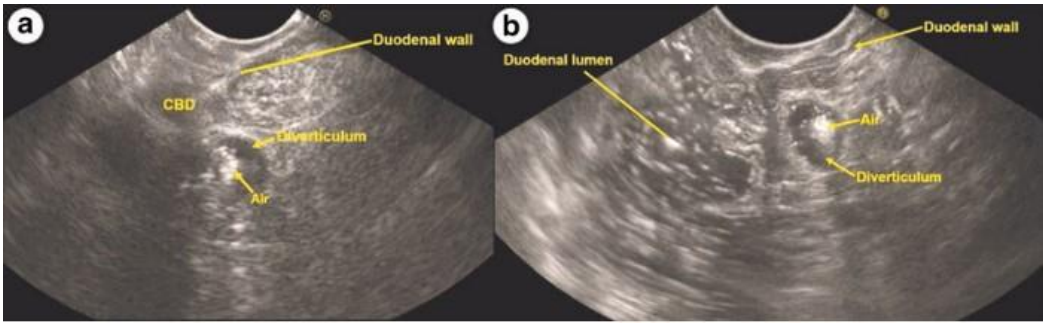

Figure (6): (a) linear endoscopic ultrasonography showing periampullary diverticulum containing air compressing lower common bile duct. (b) Endoscopic ultrasonography from descending duodenum showing a duodenal diverticulum containing echogenic air droplets near ampulla **(14)**

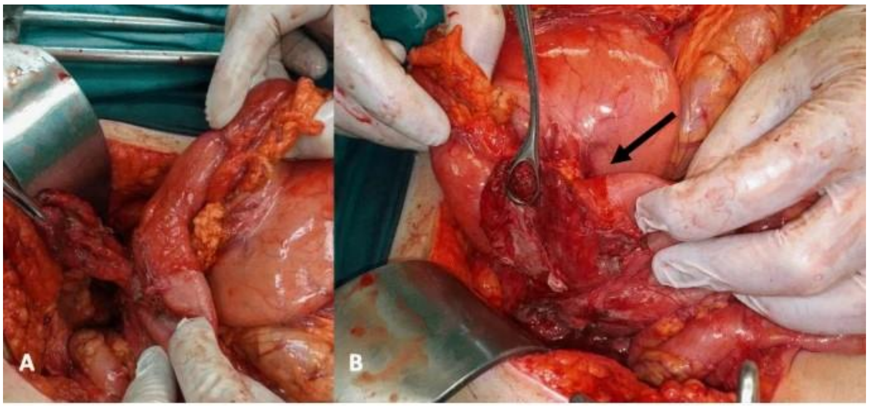

Figure (7): Intra-operative view of the perforated duodenal diverticulum, a) Anterior view, b) Posterior view, where the site of the perforation was found (arrow), and the diverticulum was covered with pseudomembranes **(15)**

ERCP success rate and periampullary diverticula

Endoscopic retrograde cholangiopancreatography (ERCP), one of the more challenging procedures performed by gastroenterologists, is associated with higher rates of complications than general endoscopy. higher-volume centers with more experienced practitioners have superior outcomes with lower adverse events than do lower-volume centers **(16)**.

One of the most technically complex aspects of ERCP is the initial step of biliary cannulation. While there are many features that can increase the level of difficulty in cannulation, a periampullary diverticulum is often recognized as a significant risk factor for failed ERCP attempts.The prevalence of PAD varies widely in the literature (3–32%) **(16)**.

The variation in location of the papilla in the setting of PAD can lead to an atypical orientation or obscured location, complicating endoscopic cannulation and stone extraction using traditional techniques. Indeed, there are many case reports highlighting innovative techniques to facilitate biliary cannulation in the setting of PAD including clip placement, the use of small diameter forceps, cap-fitted forward viewing endoscopy, and a reverse guide wire technique **(17)**.

Further, there is concern for both orientation and length of sphincterotomy when the typical landmarks are not present, due to the diverticulum. The extent of this difficulty in biliary cannulation and the potential for adverse events is not fully known, with some conflicting results in the established literature. Some authors have also argued that cannulation may actually be easier in setting of PAD, once the papilla has been identified **(16)**.

In early studies, although the success rate of ERCP in the setting of PAD was lower than those without PAD, the overall success rates (in absence of PAD) were lower than are currently generally expected, suggesting that older techniques or equipment may have contributed to the outcomes. Indeed, It was suggest that these older studies were primarily responsible for the significant reduction in success rates in ERCP with periampullary diverticula. Thus, despite their overall finding, they argue that newer ERCP accessories combined with high-volume expert practitioners likely lead to equivalent cannulation rates **(16)**.

Successful ERCP includes not just cannulation but also completion of therapy, often including stone extraction. Large stone removal can be difficult in the setting of PAD, when the altered anatomy and concern for perforation may limit the sphincterotomy length. The literature also supports a reduced rate of successful stone removal in patients with PAD with endoscopic sphincterotomy alone. It is reasonable to estimate that this may have contributed to the less successful ERCPs in earlier studies, when balloon sphincteroplasty, endoscopic hydraulic lithotripsy, and other techniques for stone extraction may not have been as widely available. A recent multicenter retrospective review stressed the considerable efficacy of balloon dilation in the extraction of large CBD stones in setting of PAD **(4)**.

ERCP in the setting of PAD has similar complication rates to those without PAD. And while the current systematic review and meta-analysis suggests the efficacy is reduced, we conjecture that had more recent studies been included, the success rates would have been comparable. Thus, we agree with the overall conclusion by Jayaraj et al. that the success of

ERCP in the setting of PAD is comparable to ERCP without PAD given sufficient expertise and experience **(18)**.

Effect of periampullary diverticulum on the technique of endoscopic papillary balloon dilatation

EPBD has several advantages over EST

First, it is less traumatic for the ampullary sphincter, which was proven in both animal and human studies. The resected specimens of pigs, obtained immediately after EPBD, showed only acute inflammation and intramucosal hemorrhage without smooth muscle disruption on histological analysis. Even after several weeks, no architectural distortion or smooth muscle disruption was noted. In human studies, histological analysis of the papilla after EPBD showed only mild to moderate inflammation and fibrosis in most patients (80-90%), while no smooth muscle disruption nor architectural distortion was observed **(19)**.

Second, EPBD may preserve papillary function. After EPBD, a mild decrease in papillary function was noted on manometry without significant difference. On the other hand, all patients who had received EST completely lost papillary function. Papillary function began to return to normal only a month after EPBD, and the basal and peak pressures of the sphincter of Oddi (SO) had significantly recovered by that time as compared with the data immediately after EPBD. In contrast, SO contraction did not recover even after one year after EST. Because the cutting method was unnecessary, the SO function was not completely lost after EPBD **(19)**.

Third, EPBD was shown to be safer for patients with bleeding tendencies. Coagulopathy under liver cirrhosis, portal hypertension or administration of anticoagulation is a known risk factor for EST-related bleeding. Because EPBD can avoid an incision, it may significantly reduce the bleeding risk and mortality in patients with liver cirrhosis and coagulopathy **(1)**.

Finally, it is favorable for those with abnormal anatomy, such as periampullary diverticulum and Billroth II gastrojejunostomy. EST is technically difficult in patients with periampullary diverticulum or Billroth II gastrojejunostomy because the cutting direction of the sphincterotome is not easy to control. Therefore, a high level of precision in the direction and length of the incision is necessary to avoid severe complication. In contrast, EPBD requires a simple technique to insert the balloon catheter into the common bile duct and inflate it. Therefore, EPBD is more suitable for patients with periampullary diverticulum or Billroth II gastrojejunostomy **(1)**.

Komatsu et al., reported on their experience of EPBD in 226 patients, and EPBD was successful in 86 patients (38.0%) with periampullary diverticulum and in two patients who had previously undergone Billroth II gastrectomy. When EST was difficult to apply due to periampullary diverticulum or prior EST, EPBD was easier and safer than EST **(20)**

The maximum diameter of the stones affects complete stone removal, especially when larger than 15 mm in length. Patients' intolerance to the procedure, unrecognized retained stones and anatomic problems such as periampullary diverticulum, situs inversus and benign distal stricture make it difficult to clear stones completely. Tortuous common bile duct and distal bile duct stricture also interfere with accessing the bile duct. In situations where deep cannulation to the bile duct may have failed, precut sphincterotomy was one of the most effective methods. Dilating the balloon immediately after the precut sphincterotomy became the method of choice before EPBD when deep cannulation failed **(21)**.

Effect of periampullary diverticulum on biliary flora and formation of CBD stones

PAD goes hand in hand with the formation of the stones, but it is still unclear what the mechanism of PAD causing the recurrence is. The possible mechanism is as follows: the inverse vertical overgrowth of bacteria and its spread to the biliary tract system; meanwhile, food was deposited in the diverticulum, forming a good medium for the bacteria **(22)**.

Common bile duct stones are a common and frequently-occurring disease and the primary common bile duct stones are mostly pigmented stones. Increasing evidence suggests that bacteria play an important role in the pathogenesis and formation of pigmented stones **(23**)

Through the study of people without biliary diseases, it has been proved that the biliary tract is sterile under normal conditions **(24)**

However, only 1% of bacteria in complex samples can be cultured, and studies have shown that even if bacteria are not cultured in patients' bile, bacterial biofilms may still exist on the surface of stone **(24)**

There are thousands of species and trillions of bacteria in the human gut, which some scholars regard as the body's "hidden organs". The research found that human health is not only related to its genetic genes but also has a subtle connection with intestinal microorganism, gene sequencing analysis has revealed the intestinal bacteria that play an incredible role, they have important effects on health, especially the gut microbes are associated with a variety of diseases, such as cardiovascular disease, intestinal disease, autoimmune disease, metabolic disease, depression, Alzheimer's, cancer as well as biliary tract disease **(25)**

The existence of parapapillary diverticulum will not only cause cholestasis but also make duodenal fluid retrograde into the bile duct so that some bacteria that can produce β-glucuronidase can be infected **(26)**

B-glucuronidase is a key enzyme that regulates the release of free bilirubin and glucuronic acid from bilirubin glucuronic acid. Free bilirubin precipitates with free calcium ions to generate calcium bilirubin, which is the main component of pigmented stones **(27)**

Calcium palmitate and fatty acids in pigmented stones (accounting for 10-20% of the content of brown pigmented stones) are related to bacterial phospholipase activity. Escherichia coli, Enterococcus, Klebsiella, Acinetobacter, and Streptococcus have β-glucuronidase activity, which is more common in pigmented stones, and Klebsiella is positively correlated with serum bilirubin levels a large proportion of these bacteria appeared in the bile of patients with periampullary diverticulum **(28)**

Lactobacillus is a kind of probiotics, but it is easy to retrograde into the bile duct because of its over-reproduction due to the relatively closed environment formed by diverticulum. In different studies, showed that Lactobacillus was rarely found in the bile of the non-diverticulum patients, while they did appear in the bile of patients with diverticulum **(29)**

Lactobacillus also has bile acid hydrolase activity, and the decrease of bile acid concentration plays an important role in the formation of pigmented stones. Its existence is bound to have a certain impact on the formation of stones **(22)**

Also, a large proportion of Veillonella was found in bile and intestinal fluid in patients with periampullary diverticulum. At present, Veillonella is associated with primary sclerosing cholangitis and Crohn's disease **(29)**

With the emergence of a new generation of sequencing technology, people can deeply study the microbial communities in different parts of the body, including those that are difficult to cultivate, and predict the metabolic function of the microbial community to find its impact on human health. The periampullary diverticulum may affect the normal anatomy of the nipple, causing compression of distal duct and expansion of the upper duct. Patients with elevated biliary pressure or biliary spasm may cause the impaired bile outflow. The size and type of PAD are associated with diameter of CBD and recurrence of choledocholithiasis. Choledocholithiasis recurrence rates of PAD I type were higher than PAD II and III type. The mean age and common bile duct diameter of patients with PAD< 15 mm were lower than those with PAD size≥15 mm **(30)**.

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