



Anticipating critical view of safety challenges in laparoscopic cholecystectomy for symptomatic cholelithiasis patients: Can we predict them earlier?

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ABSTRACT

Objective: Laparoscopic cholecystectomy (LC) is the gold standard treatment for symptomatic cholelithiasis. Identifying the critical view of safety (CVS) is crucial in this procedure to prevent complications, but achieving CVS can be challenging, necessitating bailout procedures. This study analyzes factors influencing CVS identification and describes bailout procedures used when CVS identification fails.

Material and Methods: We collected data from symptomatic cholelithiasis patients undergoing LC at Cipto Mangunkusumo Hospital from January to October 2023. Factors contributing to CVS identification failure were analyzed, and bailout procedures were described.

Results: Among 107 symptomatic cholelithiasis patients, the mean age was 50.38 years, with the majority being female (55.14% of whom were female). CVS was identified in 88 patients (82.24%). Univariate analysis showed that history of endoscopic retrograde cholangiopancreatography (ERCP) [odds ratio (OR) 5.46], Bile duct (BD) stent (OR 16.53), and diagnosis of cholecystitis (acute, OR 6.17; chronic, OR 4.00) significantly increased CVS identification failure risk. Multivariate analysis identified BD stent as the only significant risk factor (OR 7.41). Higher failure rates were associated with Parkland scores of 4-5, Nassar scores of 4, and G10 scores of 4-5. Among those with CVS identification failure, 5 completed cholecystectomy via top-down approach, 6 underwent subtotal fenestrating cholecystectomy, 6 underwent subtotal reconstituting cholecystectomy, and 2 converted to open cholecystectomy.

Conclusion: Predicting CVS identification failure using preoperative parameters and intraoperative scoring systems is crucial for anticipating surgical complexity and ensuring timely intervention. History of ERCP, BD stent presence, and cholecystitis diagnosis were significant predictors of CVS identification failure. Intraoperative scoring systems reliably predicted CVS identification failure.

Keywords: Bailout procedures, cholelithiasis, critical view of safety, laparoscopic cholecystectomy, risk factors

INTRODUCTION

Cholelithiasis is a common condition encountered in digestive surgery. While the majority of patients with cholelithiasis remain asymptomatic, approximately 1-2% develop symptoms in a year and 20% experience symptoms over a 15-year period. Symptoms of cholelithiasis manifest as a consequence of stone migration to either the cystic duct or common bile duct (CBD), thereby inciting biliary colic pain. Left untreated, this condition can escalate to cholecystitis, perpetuating discomfort and complications (1).

Presently, the gold standard intervention for symptomatic cholelithiasis patients entails laparoscopic cholecystectomy (LC) (2). However, to circumvent potential procedural complications, notably injury to the CBD and major blood vessels, meticulous identification of critical anatomical structures is paramount (3). The concept of the critical view of safety (CVS), pioneered by Strasberg, encompasses three defining criteria: (1) Visualization of only two structures unequivocally connected to the gallbladder, (2) separation of the lower one-third of the gallbladder from the liver to expose the cystic plate, and (3) absolute clarity of the hepatocystic triangle, ensuring unobstructed visualization of all cystic structures (4).

However, identifying the CVS is not always straightforward. Several factors can make visualization challenging, including inflammation, bleeding, and adhesions, which obscure critical anatomical structures and increase the risk of misidentification.

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Given these challenges, predicting the likelihood of CVS failure is crucial in laparoscopic cholecystectomy. Early recognition of potential difficulties allows for timely expert consultation, better anticipation of complications, and adequate preparation for alternative bailout strategies.

This study aims to identify the risk factors associated with failure to achieve CVS during LC in symptomatic cholelithiasis patients. We also describe the bailout strategies used in these cases, such as fundic (top-down) approach, subtotal cholecystectomy, and conversion to open surgery. Early recognition of CVS failure is essential to minimize complications and improve patient safety.

MATERIAL and METHODS

Data Collection

This study was an observational case-control study conducted at Cipto Mangunkusumo Hospital, the main referral hospital in Indonesia. We applied total sampling by including all symptomatic cholelithiasis patients who underwent LC from January to October 2023.

Data were collected from medical records, which included basic characteristics such as gender and age, as well as medical history, including prior endoscopic retrograde cholangiopancreatography (ERCP), BD stent placement, diagnosis of cholecystitis, and other comorbidities. Intraoperative scoring was also documented, including the Parkland grading scale, Nassar scale, and G10 scoring system. In cases of CVS identification failure, we documented the bailout strategies used, such as the fundibular approach (top-down), subtotal cholecystectomy, and conversion to open cholecystectomy.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 24. Patients were divided into two groups based on whether CVS identification was achieved or not. Variables were categorized into preoperative findings and intraoperative scoring, and comparisons were made between the two groups. For preoperative findings, we analyzed gender, age, ERCP history, BD stent placement, and cholecystitis diagnosis to assess any significant differences between the groups, while categorical variables were further analyzed to calculate their respective odds ratios (OR). Variables that demonstrated significant differences, including history of ERCP, BD stent placement, and cholecystitis diagnosis, were then subjected to multivariate analysis to obtain adjusted ORs. Comorbid variables were presented descriptively.

Intraoperative scoring comparisons were conducted between the CVS-identified and CVS-unidentified groups. The Parkland, Nassar, and G10 scoring systems were categorized into two groups: Low scores (1-3) and high scores (4-5). Multivariate

analysis was then performed to obtain adjusted ORs for these intraoperative variables. Among the 19 cases with CVS identification failure, the bailout strategies used were shown descriptively. Lastly, surgical outcomes, including surgery duration and intraoperative bleeding volume, were compared between the CVS-identified and CVS-unidentified groups.

Surgical Technique

The patient was placed in a supine position under general anesthesia. Following asepsis and antisepsis procedures, a 10-mm trocar was inserted at the subumbilical site using the Hasson technique. Carbon dioxide insufflation was then initiated to establish pneumoperitoneum. The patient was subsequently repositioned into a reverse Trendelenburg position with a left tilt to optimize exposure of the gallbladder and hepatobiliary structures. A second 10-mm trocar was introduced at the subxiphoid region, followed by the placement of a 5-mm trocar approximately 4 cm below the right costal margin, parallel to the midclavicular line.

The gallbladder was identified, and dissection was initiated at its lower one-third to separate it from the liver, thereby exposing the cystic plate. The CVS was then achieved by ensuring the identification of only two structures leading to the gallbladder: The cystic artery and the cystic duct. Additionally, the hepatocystic triangle was clearly delineated, bordered superiorly by the inferior edge of the liver, medially by the common hepatic duct, and laterally by the cystic duct. All fat and fibrous tissue surrounding the cystic duct and artery was carefully cleared before proceeding with ligation. Once CVS was confirmed, the cystic artery and cystic duct were securely clipped and then transected.

Following ductal and arterial division, the gallbladder was carefully freed from the liver bed using electrocautery and retrieved using an endobag to prevent bile spillage. Hemostasis was ensured before desufflation of CO₂ and removal of trocars. Finally, the surgical site was closed appropriately.

LC was performed by at least two surgeons specializing in hepato-pancreato-biliary surgery, each with experience in over 300 laparoscopic cholecystectomies.

Intraoperative Scoring

The Parkland grading system categorizes the difficulty of LC based on intraoperative findings. Grade 1 represents a normal gallbladder with no adhesions, while Grade 2 involves minor adhesions at the gallbladder neck. Grade 3 includes signs of inflammation, such as hyperemia, peri-cholecystic fluid, body adhesions, or gallbladder distension. Grade 4 involves extensive adhesions obscuring most of the gallbladder or cases with abnormal liver anatomy, intrahepatic gallbladder, or impacted stones (Mirizzi syndrome). Grade 5 represents the most severe

cases, including perforation, necrosis, or complete inability to visualize the gallbladder due to dense adhesions (5).

The G10 scoring system evaluates LC complexity using a maximum score of 10, based on eight parameters: Gallbladder adhesion, distended or contracted gallbladder, inability to grasp without decompression, stone >1 cm impacted in Hartmann's pouch, body mass index >30, adhesions from previous surgery, presence of free bile or pus outside the gallbladder, and presence of a fistula. A higher score indicates a more challenging surgical procedure (6).

The Nassar grading system assesses surgical difficulty based on three criteria: Gallbladder characteristics, cystic pedicle condition, and adhesions. Grade 1 represents an easily dissectible gallbladder with a thin, clear cystic pedicle and minimal adhesions. Grade 2 involves a packed gallbladder or mucocele, a fat-laden cystic pedicle, and simple adhesions. Grade 3 indicates a contracted or fibrotic gallbladder with acute cholecystitis, an abnormal cystic pedicle, and dense adhesions. Grade 4 represents the most complex cases, characterized by a completely obscured gallbladder, empyema, gangrene, or a mass along with dense adhesions, making dissection significantly challenging (7).

Intraoperative scoring was determined by consensus between the operator and assistant.

Ethics Statement

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, with approval number DP.04.03/D.IX.1.23/222/2025, dated April 14th, 2025.

RESULTS

There were 107 symptomatic cholelithiasis patients who underwent LC. The mean age of the patients was 50.38 [95% confidence interval (CI) 47.60-53.15], and the majority were female (55.14%). In 88 patients (82.24%), the CVS was successfully identified, while in 19 patients (17.76%), it was not. There was no significant difference in gender and age between the identified and unidentified CVS groups (Table 1).

Forty-eight patients (44.86%) had a history of previous ERCP, and 10 patients (9.43%) had a BD stent. The history of ERCP and BD stent placement has a significant association with the successful identification of CVS. Fifty-nine patients (55.14%) did not have cholecystitis, 11 (10.28%) had acute cholecystitis, and 37 (34.58%) had chronic cholecystitis. There was a significant association between the diagnosis of cholecystitis and the success of CVS identification (Table 1). Post hoc analysis showed significant differences in proportions between those with acute or chronic cholecystitis and those without cholecystitis, with p-values of 0.027 and 0.021, respectively. Multivariate analysis showed that only BD stent placement was a significant independent risk factor for the failure to identify CVS ($p=0.018$; OR 7.41, 95% CI 1.40-40.00; Table 2).

Other pathological findings were observed in both the gallbladder and surrounding structures, as shown in Table 3. Patients with Mirizzi syndrome and gallbladder empyema had a higher proportion of CVS identification failure. In addition, cystic duct was successfully identified in all patients with other pathologies, such as gallbladder carcinoma, gallbladder polyp, pancreatitis, and hepatic cirrhosis.

Table 1. Univariate analysis of preoperative parameters

Variables	CVS identified (n=88)	CVS unidentified (n=19)	p-value	OR (CI 95%)
Gender				
Male	37	11	0.315	1.90 (0.69-5.17)
Female	51	8		
Age (years)	50.00±14.88	52.11±12.76	0.568	-
History of ERCP				
No	63	6	0.002*	5.46 (1.87-15.96)
Yes	25	13		
BD stent				
No	85	12	<0.001*	16.53 (3.76-72.71)
Yes	3	7		
Cholecystitis diagnosis on admission				
No	54	5	0.016*	-
Acute	7	4		6.17 (1.33-28.57)
Chronic	27	10		4.00 (1.24-12.87)

*: $p<0.05$ is considered significant, CVS: Critical view of safety, BD: Bile duct, OR: Odds ratio, CI: Confidence interval, ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2. Multivariate analysis of preoperative parameters

Variables	p-value	OR (CI 95%)
History of ERCP	0.176	2.41 (0.67-8.62)
BD stent	0.018*	7.41 (1.40-40.00)
Cholecystitis diagnosis on admission		
Acute	0.090	4.35 (0.80-23.81)
Chronic	0.167	2.49 (0.68-9.01)

*: p<0.05 is considered significant, BD: Bile duct, OR: Odds ratio, CI: Confidence interval, ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3. Patient's comorbid

Comorbid	CVS identified	CVS unidentified
Mirizzi syndrome type I (n=1)	0	1
Mirizzi syndrome type II (n=1)	0	1
Mirizzi syndrome type III (n=1)	0	1
Gallbladder empyema (n=3)	1	2
Gallbladder carcinoma (n=2)	2	0
Gallbladder polyp, cholesterosis (n=1)	1	0
Pancreatitis (n=3)	3	0
Hepatic cirrhosis (n=2)	2	0

CVS: Critical view of safety.

Table 4. Intraoperative scoring of cholecystectomy complexity

Intraoperative scoring	CVS identified (n=88)	CVS unidentified (n=19)
Parkland		
1	48	0
2	10	0
3	21	4
4	8	9
5	1	6
Nassar		
1	54	0
2	17	0
3	14	10
4	3	9
G10		
1	59	0
2	19	0
3	6	4
4	4	14
5	0	1

CVS: Critical view of safety.

Table 4 presents the intraoperative scoring results of Parkland, Nassar, and G10, along with the proportion of successful CVS identification for each score. All patients with Parkland scores of 1-2 (58 subjects), Nassar scores of 1-2 (71 subjects), and G10 scores of 1-2 (78 subjects) had successful CVS identification. However, patients with a Parkland score of 4-5, a Nassar score of 4, and a G10 score of 4-5 had a higher proportion of identification failure compared to other scoring ranges. Multivariate analysis showed that Parkland scores of 4-5 and G10 scores of 4-5 significantly increased the risk of CVS identification failure with ORs of 18.92 and 48.11, respectively, while a Nassar score of 4 was not significant (Table 5).

Patients with CVS identification failure (19 subjects) underwent bailout procedures. Initially, all patients underwent the top-down procedure. If cholecystectomy was still not feasible, patients underwent subtotal cholecystectomy. There are two types of subtotal cholecystectomy: Fenestrating type, where the remnant gallbladder is left open, and reconstituting type, where the remnant gallbladder is sutured closed. Five subjects successfully underwent cholecystectomy with the top-down approach. Among the 14 subjects in whom the top-down approach to cholecystectomy failed, 6 underwent subtotal fenestrating cholecystectomy, 6 underwent subtotal reconstituting cholecystectomy, and 2 underwent conversion to OC (Table 6). Conversion to OC was performed due to uncontrolled bleeding during surgery.

There were significant differences in the duration of surgery and intraoperative bleeding between patients with successful CVS identification and those with CVS identification failure (Table 7).

DISCUSSION

Symptomatic gallstones are one of the indications for LC. The CVS serves as a crucial intraoperative marker in LC procedures. Successful identification of the cystic duct, CBD, and common hepatic artery (CVS) is imperative for reducing iatrogenic complications, such as injury to the CBD and large blood vessels, which are associated with high mortality and morbidity rates (4). To date, there have been few studies addressing the failure to identify the CVS in LC among patients with symptomatic gallstones.

In this study, the success rate of identifying the CVS was 82.24%. Out of 48 male patients, 11 (22.92%) experienced CVS identification failure, whereas 8 out of 59 female patients (13.56%) experienced failure. There was no significant difference in the success rate of CVS identification between the two groups. The majority of previous studies have reported a higher incidence of CVS identification failure in male patients, while some have found no significant difference between genders, as observed in this study (8-13). Male patients have a higher risk of failing CVS identification primarily due to the increased

Table 5. Univariate and multivariate analysis of intraoperative scoring

Intraoperative scoring	Univariate		Multivariate	
	p-value	OR (CI 95%)	p-value	OR (CI 95%)
Parkland 4-5	<0.001*	32.92 (8.96-120.87)	0.004*	18.92 (2.58-138.68)
Nassar 4	<0.001*	25.50 (5.91-110.00)	0.474	0.38 (0.03-5.35)
G10 4-5	<0.001*	78.75 (17.73-349.72)	<0.001*	48.11 (7.06-328.00)

*: p<0.05 is considered significant, CI: Confidence interval, OR: Odds ratio.

Table 6. Bailout procedure

Bailout procedures	Frequency (n=19)
Completed top-down	5 (26.31%)
Subtotal fenestrating	6 (31.58%)
Subtotal reconstituting	6 (31.58%)
Conversion to open cholecystectomy	2 (10.53%)

Table 7. Comparison of surgery duration and intraoperative bleeding

Variables	CVS identified	CVS unidentified	p-value
Duration (minutes)	130 (120-180)	180 (120-240)	0.019*
Bleeding (cc)	5 (3-10)	20 (10-50)	0.001*

*: p<0.05 is considered significant, CVS: Critical view of safety.

incidence of acute cholecystitis and its sequelae, which lead to intense inflammation and firm adhesions that obscure anatomical details. Additionally, males tend to have a higher pain threshold, leading to delayed medical consultation and subsequent anatomical changes in the gallbladder that further complicate dissection and identification. However, it is the underlying cholecystitis rather than male sex itself that serves as the main contributing factor (13,14). The mean age of patients who experienced CVS identification failure was 52.11, while the mean age of those who succeeded was 50.00. There was no significant difference between the two groups.

Previous bile duct interventions, including ERCP and bile duct stent placement, were found to significantly increase the risk of CVS identification failure ($p=0.002$ and $p<0.001$, respectively). Multivariate analysis identified bile duct stent placement as an independent risk factor, with an OR of 7.41 (95% CI 1.40-40.00). These findings are consistent with previous studies, such as that of Nassar et al. (15) which reported that a history of gallbladder intervention was associated with an increased risk of CVS identification failure (OR 11.11), with ERCP specifically contributing an OR of 9.08. Similarly, Nagata et al. (11) demonstrated that prior biliary drainage significantly increased the likelihood of CVS identification failure. The increased risk is due to anatomical changes from these interventions, such as fibrosis, scarring, and adhesions, which hide key landmarks. Additionally, ERCP-related changes may promote bacterial

colonization, leading to chronic inflammation and further complicating dissection. These factors collectively contribute to the difficulty in achieving a clear CVS (11,15,16).

The diagnosis of cholecystitis also significantly affects the failure of CVS identification ($p=0.016$), although multivariate analysis yielded non-significant results with an OR of 4.35 (95% CI 0.80-23.81) for acute cholecystitis and OR of 2.49 (95% CI 0.68-9.01) for chronic cholecystitis. Acute cholecystitis increases the risk of failure in achieving the CVS due to the presence of significant inflammation, edema, and increased vascularity, which lead to tissue adhesions between the gallbladder and surrounding structures. These factors obscure anatomical landmarks, making dissection more difficult and increasing the likelihood of CVS identification failure. Similarly, chronic cholecystitis contributes to CVS failure through long-standing inflammation that results in fibrosis, scarring, and gallbladder contraction (16,17).

Three patients experienced Mirizzi syndrome, classified as type I, II, and III, with one patient in each type. All three patients failed in CVS identification. Similarly, two out of three patients with gallbladder empyema failed to identify the CVS. A study by Nassar et al. (15) showed comparable results where Mirizzi syndrome and gallbladder empyema increased the risk with ORs of 20.00 and 33.33, respectively. Both conditions are associated with significant anatomical defects in biliary structures, thereby increasing the risk of CVS identification failure (17,18). Patients with other comorbid conditions, such as gallbladder carcinoma, cholesterosis, pancreatitis, and hepatic cirrhosis, were able to identify CVS successfully.

Based on our intraoperative gallbladder complexity scoring, patients with Parkland scores of 1-2, Nassar scores of 1-2, and G10 scores of 1-2 did not experience CVS identification failure. However, patients with Parkland scores of 4-5, Nassar scores of 4, and G10 scores of 4-5 were at increased risk of CVS identification failure, although only Parkland scores of 4-5 and G10 scores of 4-5 showed significance in multivariate analysis. Studies by Gupta et al. (9) and Nassar et al. (15) also observed a significant decrease in success rates with increasing gallbladder complexity scores.

According to a study by Nassar et al. (15), early identification of the likelihood of CVS identification failure is necessary, comprising preoperative prediction and intraoperative grading

(15). This is to expedite operation time, considering studies by Mischinger HJ that show a fourfold increase in perioperative complications in patients with operation durations exceeding 2 hours, compared to those with durations of 30-60 minutes (19-22).

Patients with identified CVS had significantly shorter operation durations and less bleeding. Similar results were also found in studies by Gupta et al. (9), Nassar et al. (15), Onoe et al. (12), and Stoica et al. (22). This emphasizes the importance of the operator's skills and underscores the need for early identification of the likelihood of CVS identification failure in surgeries.

Patients who experience CVS identification failure will undergo alternate strategies. The fundus-down, also called fundus-first or top-down approach, is the first choice in the bailout strategy, involving dissection from the fundus towards the cystic duct and cystic artery (19-22). A variation of the fundus-down approach, called the lateral dorsal infundibular approach, starts with fenestration between the cystic plate and the gallbladder wall, followed by dissection cephalically and then caudally towards the cystic duct (19). This approach is performed when there is strong adhesion of the gallbladder to the liver, making traction impossible. Among the 19 patients undergoing the top-down procedure, five successfully underwent cholecystectomy, with one of them utilizing the lateral dorsal infundibular approach.

If with both techniques the cystic duct and cystic artery cannot be isolated, rendering total cholecystectomy unfeasible, subtotal cholecystectomy may be considered (5). Subtotal cholecystectomy has been proven to reduce bile duct injury rates (19). There are two subtypes of subtotal cholecystectomy: Reconstructive, where the remaining part of the gallbladder is closed, and fenestrated, where the remaining part is left open, while the inner mouth of the cystic duct is sutured closed. Among the 14 patients who failed cholecystectomy with the top-down approach, 12 underwent subtotal cholecystectomy, with 6 using the fenestrating type, and 6 using the reconstituting type.

Conversion to open surgery is employed to prevent iatrogenic injury or to rectify existing injuries. In situations where the Calot triangle cannot be visualized, anatomical conditions remain unclear, and operation duration exceeds 30-60 minutes with no significant progress, conversion to open surgery may be considered. Likewise, if injuries have already occurred, such as bile duct injury or massive bleeding, conversion to open surgery may also be contemplated (5,23-25). In this study, 2 patients underwent conversion to open surgery due to uncontrolled bleeding. One patient experienced bleeding during the top-down approach, resulting in bleeding in the liver bed, which could not be controlled. The bleeding originated from variations in the anatomy of the hepatic artery branches or the right portal vein. This patient had Mirizzi syndrome type 2 with Parkland,

Nassar, and G10 scores of 4. Another patient underwent the top-down approach and then underwent subtotal cholecystectomy. However, during the dissection of the omentum to identify the Hartmann pouch, an injury occurred to a branch of the right portal vein, leading to uncontrollable bleeding. This patient had Parkland, Nassar, and G10 scores of 5, 4, and 4, respectively.

Study Limitations

This study has several limitations. Because this is a single-center study conducted at a tertiary referral hospital, the findings may not be generalizable to other institutions with different case complexity, surgical expertise, and healthcare settings, such as community or secondary hospitals. Multicenter studies are needed to validate these findings across diverse clinical environments. Additionally, this study focused on preoperative and intraoperative factors and immediate postoperative outcomes; it did not assess long-term complications such as bile duct injury, strictures, or symptom recurrence, which are important to understand the full impact on patient outcomes and quality of life. Lastly, the relatively small sample size may limit the statistical power of the multivariate analysis, potentially overlooking significant associations, thus, larger studies are needed to confirm the identified risk factors.

CONCLUSION

A history of biliary interventions—particularly ERCP and BD stent placement—and a diagnosis of cholecystitis on admission were identified as significant preoperative predictors of CVS identification failure, with BD stent placement being an independent risk factor. Intraoperative findings such as Mirizzi syndrome and gallbladder empyema were also associated with a higher likelihood of failure. Additionally, high scores (≥ 4) in intraoperative scoring systems like Parkland, Nassar, and G10 reliably predicted CVS identification difficulty.

These findings highlight the importance of thorough preoperative assessment to anticipate challenging cases. Surgeons should be especially cautious in patients with these risk factors, and be prepared to implement appropriate bailout strategies or seek expert assistance when necessary. High intraoperative scores should prompt early intraoperative decision-making to avoid complications and improve patient safety.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, with approval number DR.04.03/D. IX.1.23/222/2025, dated April 14th, 2025.

Informed Consent: Written informed consent was obtained from all patients prior to their inclusion in the study, including consent for the use of anonymized data for publication.

Footnotes

Author Contributions

Concept - A.N.L.L.; Design - A.N.L.L., V.M.G.M., I.J.; Data Collection or Processing - F.I., L.S., A.S.P.; Materials - W.S.J., T.J.M.L., V.M.G.M.; Analysis or Interpretation - A.N.L.L., Y.M., V.M.G.M.; Literature Search - D.N.W., I.J., V.M.G.M.; Critical Review - W.S.K., T.J.M.L., Y.M.; Writing - A.N.L.L., I.J., D.N.W.

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