Journal of Surgery
Kay TJ, et al. J Surg 8: 1968
www.doi.org/10.29011/2575-9760.001968
www.gavinpublishers.com
Research Article

Challenges in Accurate Clinical Prediction of Gangrenous Cholecystitis: A Single-Centre Retrospective Analysis of Operative Cases

Tegan J Kay*, Lauren Wallace, Natarssha Ryland, Nicholas Bull

Department of General Surgery, Royal Melbourne Hospital, Parkville VIC 3052, Australia

***Corresponding author:** Tegan J Kay, Department of General Surgery, Royal Melbourne Hospital, Parkville VIC 3052, Australia

Citation: Kay TJ, Wallace L, Ryland N, Bull N (2023) Challenges in Accurate Clinical Prediction of Gangrenous Cholecystitis: A Single-Centre Retrospective Analysis of Operative Cases. J Surg 8: 1968 DOI: 10.29011/2575-9760.001968

Received Date: 23 December, 2023; **Accepted Date:** 26 December, 2023; **Published Date:** 28 December, 2023

Abstract

Introduction: Gangrenous cholecystitis is a severe form of acute cholecystitis with significantly higher mortality. However, pre-operative diagnosis remains challenging. Greater understanding of the clinical presentation and associated risk factors is likely to aid surgical teams in early recognition and expedient operative management to improve outcomes.

Method: Retrospective data on presentation, investigations and outcomes was collected for patients with a histological diagnosis of gangrenous cholecystitis. Comparative analysis using data from patients with non-gangrenous acute cholecystitis was peformed to identify relevant risk factors.

Results: 61 patients with gangrenous cholecystitis were identified over a 5 year period. Most common symptoms were pain (98.4%), nausea or vomiting (70.5%) and subjective fevers (26.2%). Radiological findings included a thickened gallbladder wall (83.6%), pericholecystic fluid (63.9%) and cholelithiasis (60.7%). Pericholecystic fluid (63.9% vs 36.0%, $p<0.05$) or an irregular wall (16.4% vs 0.0%, $p<0.05$) were findings significantly higher in those with gangrenous cholecystitis. Patients with gangrenous cholecystitis were more likely to be male (57.4% vs 39.3%, $p<0.05$), report subjective fevers (26.2% vs 9.5%, $p<0.05$) and had a higher WCC (14.5 vs 11.3, $p<0.0001$) or CRP (139.8 vs 50.0, $p<0.0001$). These patients were also operated on sooner (1.7 days vs 2.3 days, $p<0.05$).

Conclusion: Gangrenous cholecystitis should be suspected in males with markedly elevated inflammatory markers, particularly when radiological investigations suggest an irregular wall or pericholecystic fluid. However, no specific risk factors, clinical features, or investigations can reliably identify this entity and surgical teams should have high suspicion with a low threshold for expedient operative intervention regardless.

Keywords: Cholecystitis; Gallbladder; Gangrenous; Risk factors

Introduction

Gangrenous cholecystitis (GC) is a severe outcome of acute cholecystitis (AC) involving partial or complete necrosis of the gallbladder wall. [1] Obstruction, most commonly of the cystic duct, increases pressure within the gallbladder resulting in increased wall tension and inflammation. [2] This leads to inadequate blood flow and sustained vascular insufficiency results in infarction of the gallbladder wall. [2] This typically occurs between days 3-5 of AC, when histological evidence of vascular thrombosis and occlusion is seen. [3] Delayed management of AC is therefore thought to result in progression to GC [4] with higher mortality in patients with increased time to hospital admission. [5] Estimated to affect between 7.1-37% of patients with AC, [6,7] GC results in higher rates of post-operative complications, [5,8,9] admission to the intensive care unit [9] and mortality. [5,10] Additionally, the presence of GC increases operative difficulty with longer case times [11,12] and a higher likelihood of conversion to open surgery. [5,8,10,11,13] To reduce the morbidity associated with GC,

early operative intervention should be the goal of management. [14] Improvements in pre-operative identification of GC has the potential to streamline clinical workflow by expediting surgical intervention and ensuring these cases are done with the support of expert acute care or hepatobiliary surgical units.

The pre-operative diagnosis of GC is a challenging clinical problem. Identified risk factors include older age, [9,10,12,13,15-18] male gender, [9,10,12,15-19] cardiovascular disease, [9,10,13,18] Diabetes Mellitus (DM), [12,13,16,17] renal disease [9] and increased inflammatory markers. [9,11-13,15,17] However, there are discrepancies within the literature and few studies have comprehensively described the presentation, investigation results and clinical outcomes of GC. We have performed a retrospective analysis of all patients presenting with GC to our hospital over a 5-year period and compared them to patients with non-gangrenous AC. The aims of this study were firstly to describe the clinical presentation, risk factors, investigation results and outcomes of patients with a histological diagnosis of GC; and secondly to identify key differences in patients with GC when compared to non-gangrenous AC.

Methods

A single-centre retrospective analysis was conducted on all patients with a diagnosis of GC over a 5 year period from the 1st of January, 2018 until the 30th of June, 2023. The inclusion criteria were as follows: all patients over the age of 18, admission under the Emergency General Surgery Unit with a histopathological diagnosis of GC. We defined GC based on the histopathological analysis of the operative specimen. Following identification of patients meeting inclusion criteria, data on clinical presentation, biochemical and radiological investigations and operative outcomes were collected using electronic medical records. To perform comparative analysis, an equal number of patients with a post-operative histopathological diagnosis of non-gangrenous AC were selected as a comparative cohort. Consecutively admitted patients under the Emergency General Surgery Unit with non-gangrenous AC in the same period were selected and similar data was collected using electronic medical records.

Statistical Analysis

All statistical analysis was performed using StataBE version 17. Descriptive statistical analysis of patients presenting with GC was performed. Subgroup analysis to investigate predictive factors was used to compare the cohorts of patients with GC to those with AC. Chi-squared test or Student's t-test were used respectively assess categorical and continuous results. Significant values were defined as a p-value less than 0.05.

Results

During the study period 61 patients were admitted under the General Surgery Unit with a histopathological diagnosis of GC. The cohort included 61 consecutive patients within the same time period with a histopathological diagnosis of non-gangrenous AC.

Presentation of GC (Table 1)

Total number with gangrenous cholecystitis	61
Median age (years)	60.3 (SD** 17.7)
Male gender	35 (57.4%)
Comorbidities	
Ischaemic Heart Disease	6 (9.8%)
Cardiac failure	1 (1.6%)
Diabetes mellitus	7 (11.5%)
Smoker	4 (6.6%)
Stroke	8 (13.1%)
Chronic Obstructive Pulmonary Disease	2 (3.3%)
Length of symptoms (days)	2.3 (SD 2.2)
Presenting symptoms	
Pain	60 (98.4%)
Nausea or vomiting	43 (70.5%)
Subjective fevers	16 (26.2%)
Change in bowel habit	15 (24.6%)
Loss of appetite	11 (18.0%)
Febrile on admission	4 (6.6%)
Tachycardia on admission	7 (11.5%)
Murphy's positive (n= 46)#	29 (63.0%)

Table 1: Describes the clinical presentation including demographics, symptoms and clinical observations of 61 patients with a histological diagnosis of gangrenous cholecystitis.*

*All numbers out of a total of n=61 unless units specified otherwise in left column, **SD = standard deviation, #Only 46 patients had Muphy's sign listed on their admission note, therefore total is out of 46

The average age of patients with GC was 60.3 years (SD 17.7) and there was a higher proportion of males (57.4%). The most common comorbidities were stroke (13.5%), DM (11.5%), ischaemic heart disease (9.8%) and current smoking (6.6%). 65.6% of patients did not have any documented comorbidities. The average length of symptoms prior to hospital presentation was 2.3 days. Symptoms included pain (98.4%), nausea and vomiting (70.5%), self-reported fevers (26.2%), change in bowel habits (24.6%) and loss of appetite (18.0%). On initial observations, 11.5% of patients were tachycardic and only 6.6% were febrile on admission. A positive murphy's sign was present in 63.0% of patients.

Biochemical and Radiological Investigations for GC (Table 2)

Bloods	
White cell count (x10^9/L)	14.5 (SD** 5.3)
C-Reactive Protein (mg/L)	129.8 (SD 127.9)
Bilirubin (µmol/L)	15.9 (SD 9.5)
Imaging	
CT	11 (18.0%)
US	24 (39.3%)
Both CT and US	25 (41%)
Nil	1 (1.7%)
Imaging findings	
Thickened wall	51 (83.6%)
Perforation	3 (4.9%)
Cholelithiasis	37 (60.7%)
Irregular wall	10 (16.4%)
Pericholecystic fluid	39 (63.9%)
Abscess	0 (0.0%)
Sludge	13 (21.3%)
Probe tenderness (n=49)#	32 (65.3%)
Diagnosis of gangrenous cholecystitis on imaging	6 (9.8%)

Table 2: Describes the biochemical and radiological investigations of 61 patients with a histological diagnosis of gangrenous cholecystitis.*

*All numbers out of a total of n=61 unless units specified otherwise in left column, **SD = standard deviation, #Only 49 patients underwent ultrasound, therefore total is out of 49 rather than full cohort.

The average White Cell Count (WCC), C-Reactive Protein (CRP) and bilirubin on admission was 14.5 x 10^9/L, 129.8mg/L and 15.9µmol/L respectively. All patients bar one underwent pre-operative imaging. 41% of patients had both Computed Tomography (CT) and Ultrasound (US) performed, while 18% had CT only and 39% had US only. The most common findings on imaging were the presence of a thickened wall (83.6%), pericholecystic fluid (63.9%), cholelithiasis (60.7%), sludge (21.3%), an irregular wall (16.4%) and perforation (4.9%). Of those 49 patients who underwent USS, 65.3% were noted to have sonographic probe tenderness. 90.2% of patients had no positive findings of gangrenous cholecystitis on pre-operative imaging.

Outcomes of GC (Table 3)

Type of operation	
Laparoscopic	54 (88.5%)
Laparoscopic converted to open	4 (6.6%)
Open	3 (4.9%)
Days from admission to operation (days)	1.7 (SD 1.3, 0-8)
Total length admission (days)	5.0 (SD 3.3, 1-17)
Death	0 (0.0%)

Table 3: Describes the operative and clinical outcomes of 61 patients with a histological diagnosis of gangrenous cholecystitis.*

*All numbers out of a total of n=61 unless units specified otherwise in left column.

The average time from admission to operative intervention was 1.7 days. The total length of admission was 5.0 days. In regards to the surgical approach for cholecystectomy, 88.5% were completed laparoscopically, 6.6% required conversion from laparoscopic to open, and 4.9% were performed open. No deaths were recorded across all admissions.

Comparative analysis to AC (Table 4)

	Non-gangrenous cholecystitis (n=61)	Gangrenous cholecystitis (n=61)	P-value
Median age (years)	56.7 (SD**18.7)	60.3 (SD 17.6)	0.274
Male Gender	24 (39.3%)	35 (57.4%)	**0.046**
Diabetes Mellitus	6 (9.8%)	7 (11.5%)	0.769
Ischaemic Heart Disease	4 (6.6%)	6 (9.8%)	0.513
Length of symptoms (days)	4.0 (SD 5.5)	2.3 (SD 2.2)	**0.029**
Symptoms			
Pain	60 (98.4%)	60 (26.2%)	0.315
Nausea and vomiting	38 (62.3%)	43 (69.4%)	0.338
Subjective fevers	6 (9.8%)	16 (26.2)	**0.019**
Loss of appetite	17 (27.9%)	11 (18.0)	0.196
Change in bowel habits	13 (21.3%)	15 (24.6%)	0.667
White cell count ($x10^9$/L)	11.3 (SD 3.4)	14.5 (SD 5.3)	**<0.001**
C-reactive protein (mg/L)	50.0 (SD 79.7)	129.8 (SD 127.9)	**<0.001**
Bilirubin (µmol/L)	13.5 (SD 8.7)	15.9 (SD 9.5)	0.161
Imaging findings			
Thickened wall	48 (78.7%)	51 (83.6%)	0.487
Perforation	1 (1.6%)	3 (4.9%)	0.309
Cholelithiasis	49 (80.3%)	37 (60.7%)	**0.017**
Irregular wall	0 (0.0%)	10 (16.4%)	**0.001**
Pericholecystic fluid	22 (36.0%)	39 (63.9%)	**0.002**
Sludge	14 (23.0%)	13 (23.3%)	0.827
Probe tenderness (n=49)	41 (83.7%)	32 (65.3%)	0.096
Days to operation (days)	2.3 (SD 1.43)	1.7 (SD 1.4)	**0.019**
Length of stay (days)	4.3 (SD 3.0)	5.0 (SD 3.3)	0.233
Operation type (laparoscopic converted to open or open)	2 (3.3%)	7 (11.5%)	0.093

Table 4: Provides a comparative analysis between patients with non-gangrenous cholecystitis versus patients with gangrenous cholecystitis.*

*All numbers out of a total of n=61 unless units specified otherwise in far left column, **SD = standard deviation.

Comparison of variables for GC versus non-gangrenous AC across presentation, investigation and outcomes can be seen in Table 4. Those with GC were more likely to be male (57.4% vs 39.3%, $p < 0.05$) and have a shorter length of symptoms prior to hospital presentation (2.3 days vs 4.0 days, $p<0.05$). Subjective fever was the only significant difference between symptoms experienced by both groups, with GC more likely to report this (25.2% vs 9.5%, $p < 0.05$). Both WCC (14.5 vs 11.3, $p<0.0001$) and CRP (139.8 vs 50.0, $p<0.0001$)

were significantly higher on admission in those with GC. The presence of pericholecystic fluid (63.9% vs 36.0%, $p<0.05$) or an irregular wall (16.4% vs 0.0%, $p<0.05$) were higher in those with GC. Gallstones were more likely to be seen in non-gangrenous AC (60.7% vs 80.3%, <0.05). There was no significant difference in the type of operation, days from admission to operation or overall length of stay between the two groups.

Discussion

We have presented a retrospective review of the operative cases for GC presenting to our institution over a five-year period. The analysis confirms male gender as an important risk factor for GC, as has been previously described. [9,10,12,15-19] Additionally, inflammatory markers were significantly elevated in the GC group, in keeping with previous literature. [6,9,11-13,15] However, almost two thirds of our patients did not have risk factors or comorbidities that have traditionally been ascribed to GC including older age, [9,12,13,15-17] cardiovascular disease [9,10,13,18] and diabetes. [12,13,16,17] The utility of imaging remains unclear with CT and US performing poorly in both detection of GC and differentiation from AC. Less than 10% of patients were diagnosed with GC on pre-operative imaging. Our results indicate that a significant proportion of patients without risk factors or positive imaging findings have a histological diagnosis of GC. Further, our comparative analysis indicates that outcomes for GC and AC are similar, which is contrary to published data suggesting higher surgical conversion rates [5,8,10,11,13] and length of hospital stay [6,9,17].

A significant proportion of patients in the in the GC cohort did not have identified risk factors or positive imaging findings. 65.6% of patients with GC has no pre-existing medical conditions. Although 98% of patients with GC presented with pain in this study, this is not always a reliable feature in cases where there is either non-localised or non-existent pain and Simeone et al. actually found a lack of Murphy's sign increased the likelihood of GC. [20] While 63% of patients in our cohort were Murphy's sign positive, this has been found to be as low as 33% in other studies. [20] Imaging may be just as misleading with only 9.8% of patients correctly diagnosed with GC on radiological investigation, despite 41.0% undergoing both CT and US and close to 99% undergoing some form of imaging pre-operatively. We found the most common radiological findings for GC were a thickened gallbladder wall, pericholecystic fluid and cholelithiasis, while the presence of pericholecystic fluid and an irregular gallbladder wall were significantly higher in those with GC when compared with non-gangrenous AC. This correlates with previous research, which identified the most specific signs on CT being gas in the wall or lumen, an irregular or absent wall and pericholecystic fluid. [21] The presence of these factors on imaging should increase surgical suspicion of GC, particularly in high risk populations.

There have been a number of proposed scores using established risk factors to aid clinicians in identifying those patients more likely to have GC. [2,4,22] Although useful, with reported sensitivities as high as 83.8%, [2] they remain of questionable clinical utility and require further validation in larger, multicentred cohorts. Importantly, the findings within this study suggest that it may be impossible to identify GC based on scoring systems utilising risk factors or investigations. These patients will only be diagnosed intra-operatively and strategies to manage difficult cholecystectomy cases are useful in this setting with a low threshold for involving senior or sub-specialist input.

We did not identify any differences in post-operative length of stay or open conversion rates between those with GC when compared to those with non-gangrenous AC. Although the majority of literature suggests the risk of conversion is significantly higher for GC, ranging from 19-64%, [5,8,10,11,13] this is not consistent across all studies. [17] Indeed, laparoscopic cholecystectomy for GC within 48 hours of presentation has been shown to significantly reduce major postoperative complications with a 36% reduction in length of stay, [12] indicating patients suspected of having GC should be given operative priority. Given the average time to operation in this study was significantly shorter in those with GC, we suspect that expedient intervention resulted in less severe findings at the time of operation, thereby decreasing technical difficulty and need for open conversion. This may be explained by the adoption of an emergency general surgery model in our hospital with widespread uptake of early cholecystectomy and prioritised theatre access. Further research may demonstrate equivalent outcomes for GC when expedient surgery is offered and cases are managed within this framework.

There are several limitations to this study. The data was collected retrospectively, which may limit accuracy. Because the critical factor in identification of GC is the histopathological findings then we have only included patients who underwent surgical intervention. It follows then that there is an unidentified cohort of patients who may have undergone medical management or percutaneous cholecystostomy either definitively or as a bridge to elective cholecystectomy. Exclusion of these patients is likely to result in a selection bias towards a younger, less-comorbid population. The sample size of 61 patients in each group is also underpowered to detect small differences in surgical outcomes.

Conclusion

GC carries significant morbidity and mortality and remains difficult to diagnose pre-operatively in patients with known AC. Our findings support a high index of suspicion for GC in male patients reporting subjective fevers on admission with markedly elevated WCC and CRP. This is further supported by findings of an irregular wall or pericholecystic fluid on radiological investigation.

There should be a low threshold for urgent surgical intervention in these patients to reduce complications and improve outcomes. However, our analysis suggests that many patients will present without risk factors or positive imaging and it may be impossible to exclude GC using current pre-operative assessments. It follows that all surgeons performing acute cholecystectomy procedures should have strategies to manage GC or escalate to senior surgical staff in the case of an unexpected intra-operative diagnosis.

References

1. Kumar V, Fausto N, Aster J (2009) Robbins & Cotran Pathologic Basis of Disease. Philadelphia W.B. Saunders Company.
2. Nguyen L, Fagan SP, Lee TC, Aoki N, Itani KM, et al. (2004) Use of a predictive equation for diagnosis of acute gangrenous cholecystitis. Am J Surg 188: 463-466.
3. Kimura Y, Takada T, Kawarada Y, Nimura Y, Hirata K, et al. (2007) Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg 14: 15-26.
4. Lee SK, Lee SC, Park JW, Kim SJ (2014) The utility of the preoperative neutrophil-to-lymphocyte ratio in predicting severe cholecystitis: a retrospective cohort study. BMC Surg 14: 100.
5. Önder A, Kapan M, Ülger BV, Oğuz A, Türkoğlu A, et al. (2015) Gangrenous cholecystitis: mortality and risk factors. Int Surg 100: 254-260.
6. Bedirli A, Sakrak O, Sözüer EM, Kerek M, Güler I (2001) Factors effecting the complications in the natural history of acute cholecystitis. Hepatogastroenterology 48: 1275-1278.
7. Fagan SP, Awad SS, Rahwan K, Hira K, Aoki N, et al. (2003) Prognostic factors for the development of gangrenous cholecystitis. Am J Surg 186: 481-485.
8. Falor AE, Zobel M, Kaji A, Neville A, De Virgilio C (2012) Admission variables predictive of gangrenous cholecystitis. Am Surg 78: 1075-1078.
9. Fang R, Yerkovich S, Chandrasegaram M (2022) Pre-operative predictive factors for gangrenous cholecystitis at an Australian quaternary cardiothoracic centre. ANZ J Surg 92: 781-786.
10. Bourikian S, Anand RJ, Aboutanos M, Wolfe LG, Ferrada P (2015) Risk factors for acute gangrenous cholecystitis in emergency general surgery patients. Am J Surg 210: 730-733.
11. Contini S, Corradi D, Busi N, Alessandri L, Pezzarossa A, et al. (2004) Can gangrenous cholecystitis be prevented?: a plea against a "wait and see" attitude. J Clin Gastroenterol 38: 710-716.
12. Ganapathi AM, Speicher PJ, Englum BR, Perez A, Tyler DS, et al. (2015) Gangrenous cholecystitis: a contemporary review. J Surg Res 197: 18-24.
13. Merriam LT, Kanaan SA, Dawes LG, Angelos P, Prystowsky JB, et al. (1999) Gangrenous cholecystitis: analysis of risk factors and experience with laparoscopic cholecystectomy. Surgery 126: 680-656.
14. Fry DE, Cox RA, Harbrecht PJ (1981) Gangrene of the gallbladder: a complication of acute cholecystitis. South Med J 74: 666-668.
15. Aydin C, Altaca G, Berber I, Tekin K, Kara M, et al. (2006) Prognostic parameters for the prediction of acute gangrenous cholecystitis. J Hepatobiliary Pancreat Surg 13: 155-159.
16. Yeh DD, Cropano C, Fagenholz P, King DR, Chang Y, et al. (2015) Gangrenous cholecystitis: Deceiving ultrasounds, significant delay in surgical consult, and increased postoperative morbidity! J Trauma Acute Care Surg 79: 812-816.
17. Nikfarjam M, Niumsawatt V, Sethu A, Fink MA, Muralidharan V, et al. (2011) Outcomes of contemporary management of gangrenous and non-gangrenous acute cholecystitis. HPB (Oxford) 13: 551-558.
18. Hunt DR, Chu FC (2000) Gangrenous cholecystitis in the laparoscopic era. Aust N Z J Surg 70: 428-430.
19. Raffee L, Kuleib S, Oteir A, Kewan T, Alawneh K, et al. (2020) Utility of leucocytes, inflammatory markers and pancreatic enzymes as indicators of gangrenous cholecystitis. Postgrad Med J 96: 134-138.
20. Simeone JF, Brink JA, Mueller PR, Compton C, Hahn PF, et al. (1989) The sonographic diagnosis of acute gangrenous cholecystitis: importance of the Murphy sign. AJR Am J Roentgenol 152: 289-290.
21. Bennett GL, Rusinek H, Lisi V, Israel GM, Krinsky GA et al. (2002) CT Findings in Acute Gangrenous Cholecystitis 178: 275-281.
22. Yacoub WN, Petrosyan M, Sehgal I, Ma Y, Chandrasoma P, et al. (2010) Prediction of patients with acute cholecystitis requiring emergent cholecystectomy: a simple score. Gastroenterol Res Pract 2010: 901739.