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ORIGINAL ARTICLE

Predicting gangrenous cholecystitis

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Abstract

Background: Gangrenous cholecystitis (GC) is often challenging to treat. The objectives of this study were to determine the accuracy of pre-operative diagnosis, to assess the rate of post-cholecystectomy complications and to assess models to predict GC.

Methods: A retrospective single-institution review identified patients undergoing a cholecystectomy. Logistic regression models were used to examine the association of variables with GC and to build risk-assessment models.

Results: Of 5812 patients undergoing a cholecystectomy, 2219 had acute, 4837 chronic and 351 GC. Surgeons diagnosed GC pre-operatively in only 9% of cases. Patients with GC had more complications, including bile-duct injury, increased estimated blood loss (EBL) and more frequent open cholecystectomies. In unadjusted analyses, variables significantly associated with GC included: age > 45 years, male gender, heart rate (HR) > 90, white blood cell count (WBC) > 13 000/mm^3, gallbladder wall thickening (GBWT) ≥ 4 mm, pericholecystic fluid (PCCF) and American Society of Anesthesiology (ASA) > 2. In adjusted analyses, age, WBC, GBWT and HR, but not gender, PCCF or ASA remained statistically significant. A 5-point scoring system was created: 0 points gave a 2% probability of GC and 5 points a 63% probability.

Conclusion: Using models can improve a diagnosis of GC pre-operatively. A prediction of GC pre-operatively may allow surgeons to be better prepared for a difficult operation.

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Introduction

Acute cholecystitis (AC) and chronic cholecystitis (CC) are commonly encountered by the general surgeon. The more severe condition GC, affects 2% to 36% of patients with AC.[1–8] While the treatment for GC is, in most cases, similar to that of non-gangrenous AC,[6,9] the presence of GC increases the risk of morbidity and mortality.[1,3]

Several previous studies have sought to identify risk factors associated with GC in order to differentiate it from simple AC and improve management.[2,3,10–12] One of these in particular, by Yacoub *et al.*,[10] offers a simple scoring system to determine the probability of GC using a number of readily available variables, such as age, white blood cell count (WBC), gallbladder wall thickening (GBWT), gender and heart rate (HR). Although most previous studies have used similar variables,[13] no independent study has yet confirmed Yacoub's scoring system. The main objectives of this study were three-fold: first to validate this scoring system in an independent dataset and to assess whether some additions to this model may improve its prediction power; second, to assess the degree to which general surgeons typically diagnose GC correctly

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pre-operatively; and third to assess the morbidity of GC. Our hypotheses were that GC is indeed predictable, that GC may not be correctly diagnosed in many cases and that the consequences of discovering GC include greater morbidity for the patient.

Methods

After obtaining Institutional Review Board approval, a retrospective chart review of consecutive patients undergoing a cholecystectomy (CCY) at Saint Agnes Hospital Center from 2000–2011 was performed. Hospital pathology and billing databases were queried and all patients undergoing CCY were identified by ICD-9 and CPT codes. Demographics, clinical, laboratory, radiological, operative, pathological and follow-up data were collected. Patients undergoing CCY for reasons other than cholecystitis, such as elective cases of biliary colic, and those undergoing CCY as an incidental part of another major operation were excluded. Cholecystitis, and type thereof, was defined at three stages: (i) pre-operatively, by the operating surgeon on the operative report; (ii) post-operatively by the surgeon on the operative report; and (iii) pathologically, by the pathologist on the final pathology report. Complications were graded according the Clavien complication grading scale.[14] Estimated blood loss (EBL) was assigned to be 50 ml if the surgeon dictated 'minimal' on the operative report. Essentially all surgeons performing a cholecystectomy in the database were general surgeons. Nearly 90% had > 3 years experience (i.e. beyond the novice learning curve for a cholecystectomy).

Statistical analysis

We used unadjusted and adjusted logistic regression models to examine the association between each of the variables used in Yacoub's model (age, gender, HR, WBC and GBWT) with GC as the main outcome. Owing to the retrospective nature of the study, some variables were missing for some patients. Age, gender and WBC were abstracted from the medical records. HR (beats per minute) was calculated as that measured in the emergency room, or operation room, or the average of the two when both were available.

We validated Yacoub's model, exactly as described by Yacoub *et al*., giving 1 point each to age > 45 years, HR > 90, and gallbladder thickness, 1.5 points to leukocytosis (>13 000 /mm^3), and 2 points to male gender. An association of each variable with the outcome, unadjusted and adjusted, was estimated. The total number of points for this model ranged from 0 (no risk factor) to 6.5 (all risk factors present). Area under the receiver-operating characteristics (ROC) curve was calculated, and goodness-of-fit measure tested for.

In addition, we conducted some exploratory analyses, with minor modifications to Yacoub's model. As detailed in the Results section, all the Yacoub variables were statistically significantly associated with GC in the adjusted models, with the exception of gender. Using the four variables that remained statistically significant in the adjusted models, a 0–5 point scoring system was created. In the adjusted model, odds ratios (ORs) for HR, WBC and GBWT were close, so they were each given one point. However, ORs for age was substantially higher. As such, age was split into three categories (≤ 45, 46 to ≤ 65 and > 65), with scores of 0, 1 and 2, respectively, for falling in these age groups. Odds ratio increments for moving from each category to the next were similar to the other three variables. Therefore, the total points for each patient could range from 0 (age ≤ 45 and no other risk factor) to 5 (age > 65 and all other risk factors positive). Area under the ROC curve was calculated and the goodness-of-fit test was done using a chi-square test. No further validation of these exploratory models was conducted.

To assess the accuracy of pre-operative diagnoses, they were compared with post-operative surgical diagnoses, and also with diagnoses made using a combination of post-operative or pathology diagnoses (combination diagnosis). The latter was done using a logical OR, such that the diagnosis was made when either the surgeon or pathologists made the diagnosis. Two-by-two tables were made, and total sensitivities, specificities and kappa values were calculated.

To compare rates of complications between GC and non-GC patients, tables were made and chi-square tests or Fisher's exact tests were done where appropriate.

Missing data were handled using listwise deletion. All statistical analyses were done using STATA statistical software (StataCorp, College Station, TX, USA), version 12.1.

Results

In all, 5812 patients underwent CCY at St. Agnes Hospital Center during the study period. Of these, 259 patients who underwent CCY as part of another major operation and 310 patients with no evidence of cholecystitis were excluded from the analysis. Of the remaining 5243 patients with a pre-operative diagnosis of cholecystitis, 2119 had AC, 4837 had CC and 351 had GC, based on either post-operative diagnosis of the surgeon or pathological diagnosis. Overall, 1398 (27%) were males and 3845 (73%) were females. The mean age (± SD) in this group was 52 (± 18) years.

Validation of the the Yacoub score in an independent dataset

Table 1 shows the unadjusted and adjusted results for the association between each of the variables used in Yacoub's model in relation to GC. In the unadjusted models, all five variables were statistically significantly related to GC: age > 45 years (OR = 3.2), HR > 90 (OR = 2.8), male gender (OR = 3.1), WBC > 13 000 (OR = 5.1) and GBWT > 4.5 mm (OR = 3.2). In adjusted analyses including all five variables, male gender (OR = 1.4) lost statistical significance, but the remaining variables, age (OR = 4.8), HR (OR = 2.0), WBC (OR = 2.8) and GBWT (OR = 2.2) remained statistically significant. The scores created using Yacoub's model ranged from 0 to 6.5. The OR [95% confidence interval (CI)] for each unit increase in the score was 1.7 (1.5–2.0). The probabilities

Table 1 Pre-operative risk factors in cholecystitis patients predicting GC

	GC (*n* = 351) n1/n2 (%)	No GC (*n* = 4892) n1/n2 (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age (>45 versus ≤ 45 years)	291/351 (83%)	2946/4892 (60%)	3.2 (2.4–4.3)	4.8 (2.2–10.6)
HR (> 90 versus ≤ 90 / min)	138/328 (33%)	384/3067 (15%)	2.8 (1.9–4.1)	2.0 (1.1–3.6)
Gender (male versus female)	178/351 (51%)	1220/4892 (25%)	3.1 (2.5–3.9)	1.4 (0.8–2.5)
WBC (> 13000 versus < 13000)	138/328 (42%)	384/3067 (13%)	5.1 (4.0–6.5)	2.8 (1.6–5.0)
GBWT (Yes versus no)	159/215 (74%)	781/1649 (47%)	3.2 (2.3–4.3)	2.2 (1.2–4.1)

GC: gangrenous cholecystitis; OR: odds ratio; CI, confidence interval; HR: heart rate; WBC: white blood cell count; GBWT: gallbladder wall thickening. Data were complete for age and gender but partially missing for other variables. For each variable, n1 shows the number with the condition (e.g. age > 45) and n2 shows the total number with data.
Odds ratios and 95% confidence intervals are obtained using logistic regression models. In the adjusted models, each variable was adjusted for other variables shown in the table. A total of 478 patients had data for all variables, from whom data were used to construct the adjusted model.

Table 2 Correspondence between probabilities of gangrenous cholecystitis versus those obtained from Yacoub's model

Score	*N*[a]	Actual probability	Predicted probability (prediction interval)[b]
0	49	0.02	0.03 (0.02–0.06)
1	105	0.06	0.06 (0.04–0.09)
1.5	10	0.10	0.07 (0.05–0.11)
2	94	0.12	0.09 (0.07–0.13)
2.5	18	0.17	0.12 (0.09–0.16)
3	45	0.09	0.15 (0.12–0.19)
3.5	25	0.24	0.19 (0.15–0.24)
4	60	0.20	0.24 (0.19–0.29)
4.5	29	0.28	0.29 (0.23–0.36)
5	11	0.36	0.35 (0.27–0.44)
5.5	21	0.48	0.41 (0.31–0.52)
6.5	11	0.55	0.55 (0.41–0.69)

[a]*N* = number of patients with each score. In all, 478 patients had complete data for all four variables.
[b]*P*-value for the chi-square goodness of fit for the model = 0.95.

predicted by the model were close to the actual probabilities, with a chi-square *P*-value for goodness-of-fit test of 0.95 (Table 2). The area under the ROC curve for this model was 0.74.

In exploratory analyses, two additional variables, presence of pericholecystic fluid (PCCF) and American Society of Anesthesiology (ASA) score > 2, which were not used by Yacoub and colleagues, were also tested. PCCF (OR = 3.5; 95% CI: 2.6–4.6) and ASA score (OR = 2.7; 95% CI: 1.7–4.4) were significantly associated with risk of GC in unadjusted analyses, but fell out of significance on adjusted analyses: PCCF (OR = 1.2; 95% CI: 0.54–2.4) and ASA score > 2 (OR = 1.6; 95% CI: 0.8–3.1).

Using the four variables that remained statistically significant in the adjusted models, an exploratory scoring system (0–5 points) was created, as described in the statistical methods section. The OR (95% CI) for each successive one unit increase in the score was 2.3 (1.9–3.0). A patient with a score of 0 had a minimal (2%) risk of having GC, and a patient with a score of 5 had a significantly elevated (63%) risk of having GC, showing the strong ability of the model to predict GC. The probabilities predicted by the model were very close to the actual probabilities, with a *P*-value for goodness-of-fit test of 0.96 (Table S1). The area under the receiver-operating-characteristics curve for this model was 0.77.

Accuracy of the surgeon's pre-operative diagnosis

To assess the real-world accuracy of the surgeon’s diagnosis regarding cholecystitis, we compared pre- with post-operative diagnoses. We also compared pre-operative diagnoses with those made using a combination of post-operative or pathology diagnoses (combination diagnosis).

Table 3 shows sensitivities (% true positive), specificities (% true negative) and kappas for pre-operative diagnoses compared with both post-operative and combination diagnoses. The surgeon’s prediction of AC or CC was accurate, whereas the prediction of GC was quite inaccurate: For AC, the concordance between pre- and postoperative and also between pre-operative and combination diagnoses were very high for AC, with kappa values of 0.89 and 0.83, respectively. For CC, the concordance was very high for pre- and post-operative diagnoses (kappa = 0.90) but not for pre-operative and combination diagnoses (kappa = 0.07), owing to a large number (n = 3167) of patients diagnosed by pathologists, but not by surgeons, as having chronic cholecystitis. For GC, the concordance was low for both pre- and post-operative diagnoses (kappa = 0.24) and for pre-operative and combination diagnoses (kappa = 0.16). Of the 351 GC cases diagnosed using post-operative or pathology, only 32 (9%) were diagnosed preoperatively.

Assessment of morbidity and mortality

Compared with patients without GC, those with GC had a six-fold increase in risk of requiring conversion from a laparoscopic to an open CCY (3.4% versus 21% rate of conversion, *P* < 0.001). Similarly, severe blood loss, defined as ≥ 500 ml, was seen in 6.7% of the GC patients versus only 1.3% of other patients (*P* < 0.001). The overall post-operative complication rate after cases of GC was 17% compared with 6.7% for non-GC cases (*P* < 0.001). Furthermore, these complications were more severe. For GC, 14% of complications were Clavien classification 3 or 4, compared with

Table 3 Comparison of pre- and post-operative diagnosis of GC

	Cases[a]		Non-Cases[a]		Kappa (standard error)
	True Positive *N* (%)[b]	False Negative *N* (%)	True Negative *N* (%)[b]	False Positive *N* (%)	
Pre- AC versus post-operative diagnosis	1747 (94%)	117 (6%)	3237 (96%)	142 (4%)	0.89 (0.01)
Pre- AC versus combination diagnosis	1797 (85%)	322 (15%)	3032 (97%)	92 (3%)	0.83 (0.01)
Pre- CC versus post-operative diagnosis	1602 (90%)	173 (10%)	3416 (98%)	52 (2%)	0.90 (0.01)
Pre-operative CC versus combination diagnosis	1649 (34%)	3188 (66%)	401 (99%)	5 (1%)	0.07 (0.01)
Pre- GC versus post-operative diagnosis	29 (15%)	171 (85%)	5039 (99%)	4 (1%)	0.24 (0.01)
Pre-operative GC versus combination diagnosis	32 (9%)	319 (91%)	4891 (100%)	1 (0%)	0.16 (0.01)

[a]Cases and non-cases were determined using either the post-operative diagnosis, or using a combination of post-operative or pathology diagnoses.
[b]Per cent true positive and per cent true negative are, respectively, equivalent to sensitivity and specificity of the pre-operative diagnoses.

7.5% for non-GC ($P < 0.001$). Importantly, the rate of bile-duct injury (BDI) was six-fold higher (1.1%) after CCY for GC, compared with non-GC cases (1.1% versus 0.18%, $P = 0.001$). The injuries in the GC cases and the non-GC cases were predominantly leaks from the cystic duct stump or aberrant ducts.

Discussion

While routine AC is often appropriately treated by general surgeons, GC poses significantly increased morbidity and is more challenging to safely treat. The current data from St. Agnes Hospital show significant increases in rates of conversion to open CCY, complications (both number and severity), EBL and BDI associated with GC. Although the rate of BDI, compared with other, more common post-CCY complications, is low in this and other series, there is still cause for alarm given how common an operation CCY is: given that the number of CCYs performed each year in the US is approaching 1 000 000, and the reported rates of BDI in the literature are 0.4% to 15%,[15–17] one can expect thousands to tens of thousands of cases of BDI to occur every year. Furthermore, given that the overall impact of BDI can be potentially severe,[18,19] this is one of the most costly complications to patients and society.

The conversion and complication rates at St. Agnes are consistent with many published reports. Nikfarjam *et al.*[3] found conversion rates of 7% for non-GC and 14% for GC, whereas Merriam *et al*[5] reported rates of 6% and 35% for non-GC and GC, respectively. The rates of 3.4% (non-GC) and 21% (GC) found in the current study confirm a significantly increased risk of open conversion associated with GC. While conversion per se should not be categorically considered a complication, similarly, and not surprisingly, the current and other studies have shown a higher rate of overall complications in GC versus non-GC, including a higher risk of peri-operative mortality.[3,13]

Given these risks, accurate pre-operative diagnosis and documentation of GC is essential. Yet, the current analysis shows that surgeons and radiologists are remarkably unsuccessful in diagnosing GC, as 91% of cases of GC were not diagnosed as such pre-operatively. If an accurate, simple and readily accessible prediction model for GC were available, arrangements could be made pre-operatively to prepare for a more difficult procedure, a higher possibility of conversion to open surgery, consideration of assistance from another colleague and a higher level of post-operative care that might be needed for a more morbid condition. Such a model, using factors immediately available to the surgeon – gender, WBC, HR, GBWT and age – was proposed by Yacoub *et al.* in a study of 245 patients.[10] The current series has largely validated that scoring system in an independent dataset, with only gender losing significance in the multivariate analysis.

There have been other efforts to determine which risk factors are most relevant in predicting GC as well: Table 4 lists several such attempts over the past 10 years, but only the Yacoub and the current studies have offered a simple scoring system. Falor *et al.*[13] have also largely confirmed the variables in the scoring system and have added serum sodium as predictive of GC, analogous to studies showing it to correlate with necrotizing soft-tissue infections. In the current series, however, serum sodium did not correlate with GC.

There are limitations to this study. In particular, the study is retrospective and therefore is subject to all the usual problems associated with such studies, such as incomplete or missing data acquired from chart reviews. For instance, post-operative complications can be difficult to track retrospectively and while GC is clearly a risk factor predictive of complications, one cannot conclude from these data that it is casual. However, causal or simply predictive, it does identify patients at risk. Similarly, prior admissions for abdominal pain in the absence of a cholecystectomy were not captured in this database of patients undergoing a cholecystectomy, so periods of treatment with antibiotics to allow inflammation to subside may have been missed. In addition, the data analysed come from a single institution, a fact that may limit widespread applicability of results and conclusions, but may also confer a benefit of uniformity. Finally, because the pre- and post-operative diagnoses come from dictated operative notes, they therefore reflect the interpretation of the operating surgeon; if a surgeon diagnoses GC postoperatively, but the pathology report

Table 4 Comparison of risk factors for GC in the literature

GC study			Risk factors (*P*-value for predicting GC)										
First Author, year[ref]	No. (%) with GC	Total no. with AC	Age (years)	Gender	DM	HR	WBC (×1000)	ALT	AP	Na	GBWT (mm)	PCCF	Scoring system
Fagan, 2003[12]	40%	113	>51 (0.04)[a]	NS	Yes (0.045)[b]	NS	>15 (0.001)[b]	>50 (0.035)[b]	>200 (0.026)[b]	NS	NS	Yes (0.11)[b]	No
Nguyen, 2004[11]	18%	98	NS	NS	Yes (<0.1)[b]	NS	>15 (<0.1)[b]	>50 (<0.1)[b]	>200 (<0.1)[b]	NS	NS	Yes (<0.1)[b]	No
Aydin, 2006[2]	10%	203	59 versus 51[c] (0.001)[a]	Male (0.005)[b]	Yes (0.005)[b]	NS	>15 (0.001)[b]	56 versus 43 (0.02)[a]	268 versus 222 (0.02)[a]	NS	6.2 versus 4.6 (0.0001)[a]	Yes (0.0001)[a]	No
Yacoub, 2010[10]	28%	245	>45 (0.019)[b]	Male (0.001)[b]	NS	>90 (0.007)[b]	>13 (0.005)[b]	NS	NS	NS	>4.5 (0.014)[b]	NS	Yes
Nikfarjam, 2011[3]	37%	290	69 versus 57 (0.001)[a]	Male (0.001)[a]	Yes (0.04)[a]	>100 (0.001)[a]	13 versus 11 (0.001)[a]	26 versus 43 (0.001)[a]	NS	NS	ND (0.03)[a]	NS	No
Falor, 2012[13]	23%	391	46 versus 39 (0.007)[a]	Male (0.001)[b]	NS	>90 (0.02)[b]	>14 (0.001)[b]	NS	NS	≤135 (0.04)[b]	NS	NS	No
Current study, 2013	*6.7%*	*5243*	*>45 (0.001), >65 (0.001)*[b]	*Male (0.001)*[a]	*NS*	*>90 (0.02)*[b]	*>13 (0.001)*[b]	*NS*	*NS*	*NS*	*>4.5 (0.007)*[b]	*Yes (0.001)*[a]	*Yes*

[a]In univariate analysis only
[b]Confirmed in multivariate analaysis
[c]X versus Y signifies GC versus non-GC.
ALT, alanine aminotransferase; AP, alkaline phosphatase; DM, diabetes mellitus; GBWT, gallbladder wall thickening; HR, heart rate; ND, not defined; NS, not significant or not shown; PCCF, pericholecystic fluid; WBC, white blood cell count.

does not, it may be because some surgeons use the term GC to refer to an exceptionally difficult CCY as opposed to true GC. In contrast, in cases where the surgeon's pre-operative diagnoses do not include GC, but the pathological diagnosis is GC, this may be as a result of the surgeon recognizing that GC has been historically difficult to predict well, and impossible to predict perfectly; knowing in addition that GC is a form of AC or CC, the surgeon may be reluctant to diagnose GC pre-operatively.

Conclusion

GC is a particularly severe form of AC/CC and is associated with markedly worse outcomes, including an increased risk of conversion rates, EBL and complications, especially BDI. Currently, the vast majority of cases of GC are not diagnosed pre-operatively. However, Yacoub's scoring system using age, gender, WBC, GBWT and HR could predict the probability of GC pre-operatively. Therefore, when GC is predicted to be likely (e.g. a score of 4 or higher, indicating a > 20% probability), one should be prepared for a difficult case and a request for colleague assistance should be considered.

Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Correspondence between probabilities of gangrenous cholecystitis versus those obtained from the simplified model.