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Biochemical predictors of complicated diverticulitis: A case-control study evaluating white cell count and C-reactive protein in the assessment of acute diverticulitis

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Ethics Committee Approval
Ethical approval granted by the Human Research Ethics Committee (HREC Australia) and site-specific approval granted by Phillis Galvin, Manager-Medical records department, Lyell McEwin Hospital, Adelaide, Australia. Date: 18/01/2018. Number: HREC/18/CALHN/38
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Acute diverticulitis represents a common surgical condition and one of the leading gastrointestinal causes of surgical admissions in Western societies. Complicated diverticulitis increases the length of the hospital stay and the risk of requiring surgical intervention. In areas of limited availability or long waiting times for CT scanning, biochemical predictors of complicated diverticulitis might be valuable. In the available literature, there is no consensus on cut-off values of C-reactive protein or the value of a white cell count in the diagnosis of complicated diverticulitis. Additional studies among different populations are required to add to the existing literature to reach a consensus on diagnostic cut-off levels of inflammatory markers to diagnose complicated diverticulitis. The aim of the present study is to evaluate the predictive value of a white cell count and C-reactive protein, and their sensitivity and specificity in differentiating complicated from uncomplicated diverticulitis.

Methods: This case-control study was performed for patients with acute diverticulitis in Lyell McEwin Hospital in Adelaide, South Australia. Data were collected for consecutive patients admitted from January 2015 to December 2017. Patients with acute diverticulitis confirmed by computed tomography were included in the study. Data of patients with complicated diverticulitis were compared to those of patients with uncomplicated diverticulitis as a control group. Patient characteristics, symptoms, number of attacks of diverticulitis, presence of immunosuppression, past history of complicated diverticulitis, inflammatory markers (white cell count and C-reactive protein), and computed tomography findings were collected and compared.

Results: A total of 106 consecutive cases were recruited for the period from 2015 to 2017. There were 44 cases of complicated diverticulitis and 62 cases with uncomplicated diverticulitis (control group). A white cell count (WCC) and C-reactive protein (CRP) were collected at the time of presentation from the clinical records and pathology reports. A receiver operating characteristic (ROC) analysis was performed and multiple cut-off values for both WCC and CRP were reported. For WCC, the area under curve (AUC) was 0.69 (0.582-0.797) with a *P*-value of 0.001. At a cut-off of 14, sensitivity was found to be 56.8% and specificity of 80.7%. The sensitivity gradually decreased and specificity gradually increased as the cut-off value increased. At 18 the sensitivity was 25% and specificity was 79%. The positive predictive value for the study sample at WCC of 18×10^9/L or above is 79.5%. For CRP, the AUC was 0.828 (0.729-0.927) with a *P*-value of <0.001. At a cut-off value of 100 mg/L, the sensitivity was 72.7% and specificity was 80.6%. Sensitivity gradually decreased and specificity increased as the cut-off increased in value. At 160 mg/L, sensitivity was 36.36% and specificity was 97.22% with a positive predictive value of 76%.

Conclusion: Contrary to what has been previously reported in the literature, we found that WCC remains a significant test in diagnosing complicated diverticulitis. A high cut-off value of 18×10^9/L is useful in predicting complicated diverticulitis with high positive predictive value. When compared to WCC, CRP is a more sensitive test in detecting complicated diverticulitis. We recognized a cut-off value of 160 mg/L to be a significant value to rule in complicated diverticulitis with a significant positive predictive value. WCC and CRP are very specific predictors of complicated diverticulitis with high positive predictive value at high cut-off values of 18×10^9/L and 160 mg/L, respectively.

Keywords: acute diverticulitis, white cell count, C-reactive protein, biochemical predictors

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Introduction

Diverticular disease represents a common surgical condition with a rising incidence in Western societies. It is expected that 30% of people above age 60 have diverticular disease. The prevalence rises to 60-80% of people above 80 years of age. Symptoms develop in 10-20% of people [1].

Both the incidence of acute diverticulitis and the number of cases requiring hospital admissions are increasing [2]. This is particularly true among the younger age group (18 - 44 years) which accounts for 82% of cases [3].

Diverticular disease is a common cause of hospital admissions, which results in a significant burden on the health care system in Western societies [4,5]. It is one of the most common gastrointestinal conditions that requires hospitalization and the leading indication for elective colon resection in the United States [6-8].

The modified Hinchey classification is a well-recognized classification system that is used to describe perforated diverticular disease. The classification includes multiple stages: Stage Ib (pericolic abscess), Stage IIa (distant abscess amenable to percutaneous drainage), Stage IIb (complex abscess associated with/without fistula), Stage III (generalized purulent peritonitis) and Stage IV (fecal peritonitis) [9].

There is no clear distinction between uncomplicated and complicated diverticulitis in terms of clinical and laboratory findings[9]. The use of inflammatory markers as biochemical predictors of complicated diverticulitis has been studied in multiple previous studies. The findings of WCC as a predictor of perforated diverticulitis are conflicting. One study found variable accuracy of WCC in predicting complicated diverticulitis [10]. Another study found no correlation between WCC and complicated diverticulitis [11]. Another report indicated that WCC was found to correlate with complicated diverticulitis, but no further diagnostic evaluation was done [12]. The diagnostic value of WCC was found to be poor with area under curve of only 0.58 in another study [13].

A great deal of research has been conducted to investigate the usefulness of C-reactive protein as an inflammatory marker in predicting complicated diverticulitis; however, there was no consensus on a cut-off level of CRP as a diagnostic test of complicated diverticulitis. Most of these studies, showed that CRP is a useful predictor in detecting complicated diverticulitis [14]. Some studies suggested CRP> 200 mg/L with a positive predictive value (PPV) of 69%. In another study CRP >200 mg/L had a PPV of 90% and negative predictive value (NPV) of 59% for complicated diverticulitis [15]. A cut-off of 150 mg/L was reported in a later study [15]. CRP was reported to be higher in patients who needed emergency surgery (171.8 mg/L) compared to those who were managed conservatively (101.5 mg/L) [11]. Another study recommended a CRP cut-off of 175 mg/L with a PPV of 36%, a NPV of 92%, a sensitivity of 61%, and a specificity of 82% [13]. This was a similar finding to other research with a CRP cut-off value of 170 mg/L to distinguish patients who needed surgery. The sensitivity was 87.5% and the specificity was 91.1% [16]. Only one report found no significant difference in CRP levels between uncomplicated and contained perforation [17].

The aim of the present study is to evaluate the predictive value of white cell count and C-reactive protein in detecting complicated diverticulitis, and their sensitivity and specificity in differentiating complicated from uncomplicated diverticulitis at different cut-off values.

Materials and methods

This case-control study was conducted in Lyell McEwin Hospital in Adelaide, South Australia. The Human Research Ethics Committee (HREC Australia) issued approval HREC/18/CALHN/38. Both HREC approval and site-specific approval were obtained following the ethical approval process guidelines. Data were obtained from records of consecutive patients admitted for inpatient management of acute diverticulitis from January 2015 to December 2017.

Patients with diverticular disease were identified by using medical condition specific codes available in hospital records. Patients with CT diagnosis of acute diverticulitis were included in the study. Patients with diverticular bleeding, no CT confirmation, and incidental diverticular disease on colonoscopy were excluded.

The study sample was divided into a case group and a control group. Patients with a Hinchey Ia diverticulitis classification were designated as “uncomplicated diverticulitis. Patients with Hinchey Ib and above were described as having “complicated diverticulitis.” This determination was made based on radiological diagnoses.

Baseline characteristics, previous diverticulitis, immunosuppression, previous complicated diverticulitis, white cell count, C-reactive protein, and computed tomography findings were obtained and reported. These parameters were extracted from the patient’s clinical, laboratory and radiology records.

Statistical analysis

Binary and continuous data were used in the study. White cell count and C-reactive protein were analyzed as continuous data. Analysis of binary variables was performed using 2 x 2 tables and calculating odds ratios with 95% confidence intervals and using Chi-squared as the test of significance. Diagnostic test analysis was performed by using receiver operating characteristic curves and area under the curve with 95% confidence intervals for both white cell count and C-reactive protein. In addition, the sensitivity, specificity, PPV, and NPV of multiple cut-off values for both white cell count and C-reactive protein were calculated and reported. The calculation of PPV and NPV was performed using the prevalence of complicated diverticulitis in the study group. This, in turn, was calculated from data of all consecutive patients admitted to the hospital with acute diverticulitis in 2015.

Results

For the period of 2015-2017, 116 consecutive cases were collected; 10 cases had no CT diagnosis and were excluded, leaving a total of 106 consecutive cases, which were recruited for the study. There were 44 cases of complicated diverticulitis and 62 cases with uncomplicated diverticulitis. Uncomplicated diverticulitis cases were allocated as the control group. Table 1 summarizes the characteristics of the study groups and other

factors that were expected to be relevant in determining outcomes.

Table 1: Characteristics of the study groups

	Complicated (Case) group	Uncomplicated (Control) group
Frequency	44	62
Sex (%)		
Male	26 (59%)	32 (52%)
Female	18 (41%)	30 (48%)
Mean age (SD)	56.7 (17)	56.2(14.6)
First episode	23 (52.3%)	24 (38.7%)
Recurrent episode	21 (47.7%)	38 (61%)
Immune suppression	3 (6.8%)	5 (8%)
Previous complicated diverticulitis	8 (18.2%)	11 (17.8%)

The inflammatory markers, namely WCC and CRP, were the biochemical markers of interest in this study. WCC and CRP at time of presentation were collected from clinical and pathology reports. ROC analysis was performed. In addition, multiple cut-off values for both WCC and CRP were reported. Sensitivity and specificity were calculated for each cut-off. PPV and NPV were calculated based on the prevalence of the complicated diverticulitis in the study population. The prevalence of complicated diverticulitis was 20%. An odds ratio with 95% confidence interval was also calculated to assess the increase in risk for each cut-off value (Table 2).

For WCC, the ROC was obtained (Figure 1). The AUC was 0.69 (0.582-0.797) with a *P*-value of 0.001. This was a statistically significant result with a fair diagnostic value. To help in recognizing appropriate diagnostic cut-off value, sensitivity and specificity along with PPV, NPV and odds ratio (OR) of multiple cut-off values were reported. Table 2 summarizes the diagnostic test parameters for cut-off values of 14, 15, 16, 17 and 18 ($\times 10^9$/L). At cut-off of 14, sensitivity was found to be 56.8% and specificity 80.7%. The sensitivity was found to gradually decrease and specificity gradually increase as the cut-off value increased. At 18 the sensitivity was 25% and specificity was 79% (Table 2). A PPV of WCC of 18 or above was present in 79.5% in the study population.

Figure 1: White cell count ROC curve

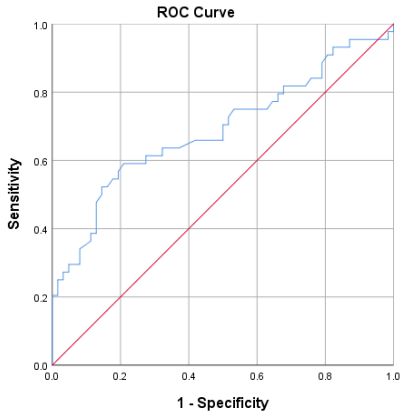


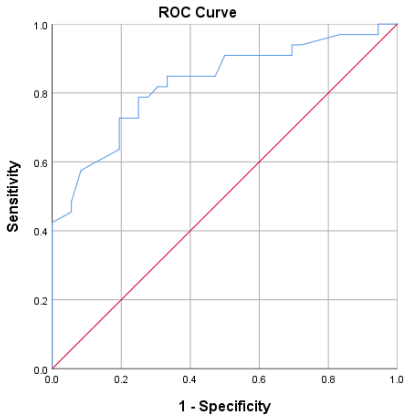
Table 2: Evaluation of multiple cut-off values of WCC and CRP in predicting complicated diverticulitis

Cut-off values	Sen	Spe	PPV	NPV	OR	CI 95%
WCC ($\times 10^9$/L)						
14	56.8	80.7	42.3	88.2	5.482	2.302 – 13.055
15	50	85.5	46.3	87.2	5.889	2.344 – 14.794
16	38.6	87.1	42.8	85	4.25	1.629 – 11.088
17	27.3	95.2	58.5	84	7.375	1.938 – 28.062
18	25	98.4	79.5	84	20.33	2.514 – 164.47
CRP (mg/L)						
100	72.7	80.6	48.3	92	11.048	3.583 – 34.067
120	57.6	91.7	63.3	89.6	14.929	3.798 – 58.676
140	45.5	94.4	67.2	87.4	14.167	2.912 – 68.927
160	36.36	97.22	76.6	85.94	20	2.42 - 166.67

Sen: sensitivity, Spe: specificity WCC: white cell count, CRP: C-reactive protein, PPV: positive predictive value, NPV: negative predictive value , OR: odds ratio, CI: confidence interval

For CRP, there were 37 missing data, and these were for patients who did not have CRP done during admission. Sixty-nine cases were available for analysis. The ROC curve was obtained as shown in Figure 2. The area under the curve was 0.828 (0.729-0.927) with a *P*-value of <0.001. This was a statically significant result with a high diagnostic value. Diagnostic test parameters of cut-off values of 100, 120, 140 and 160 (mg/L) were reported (Table 2). At cut-off value of 100 the sensitivity was 72.7% and the specificity was 80.6%. Sensitivity decreased and specificity increased as the cut-off increased in value. At 160 mg/L, sensitivity was 36.36% and specificity was 97.22% with PPV of 76% in the study population.

Figure 2: C-reactive protein ROC curve



Discussion

In this study we examined the diagnostic value of both WCC and CRP in detecting complicated diverticulitis. We found that both WCC and CRP have a diagnostic value in predicting complicated diverticulitis. The AUC for WCC was 0.69 (0.582-0.797) and the *P*-value was 0.001. This represents a significant finding compared to the existing literature. Accordingly, WCC has a fair value as a predictive test of complicated diverticulitis. This result supported the usefulness of WCC as a predictive test of complicated diverticulitis. This finding was contrary to current literature conclusions of no correlation, variable accuracy, or poor value of WCC in predicting complicated diverticulitis [10,11,13].

CRP as a predictive test of complicated diverticulitis had a higher AUC of 0.828 (0.729-0.927) with a *P*-value of <0.001. This represents a very significant result and high value in predicting complicated diverticulitis. This finding confirms similar results of previous studies of high value of CRP as a predictor of complicated diverticulitis [11,13-16].

Choosing a effective cut-off value for use in clinical practice depends on the clinical scenario. It must be determined whether a higher sensitivity is required to detect more cases of complicated diverticulitis or a higher specificity is needed to achieve greater accuracy in predicting complicated diverticulitis.

For WCC, a cut-off value of 18 in the study population had a specificity of 98.4% with positive predictive value of 79.5%. This means the chances of having complicated diverticulitis for cases with WCC of 18 or above is almost 80% within the study population. At this cut-off value, the odds of having complicated diverticulitis are 20 times higher than that of uncomplicated diverticulitis. Sensitivity at this cut-off is only

25%, making this cut-off value more useful in determining complicated diverticulitis.

For CRP, all the cut-offs examined showed higher sensitivities compared to those for WCC. At a cut-off of 160, specificity was 97.22% and a positive predictive value of 76.6% was seen in the study population. The means that at CRP of 160 mg/L and above, the chances of having complicated diverticulitis is 76.6%. Once again, the estimated odds of having complicated diverticulitis were 20 times the odds of uncomplicated diverticulitis in the study population. Sensitivity at this cut-off was only 36%, making this cut-off value more useful in ruling on cases of complicated diverticulitis. Compared to the current literature we found that a CRP cut-off value of 160 mg/L has a significant specificity and PPV, making it useful in clinical practice as a predictor of complicated diverticulitis. This result was very close to studies in the available literature with findings of a cut-off of 150 mg/L or slightly higher 175 mg/L, but significantly lower than the cut-off of other study findings of 200 mg/L [11,13-16].

Both WCC and CRP are highly specific tests in predicting complicated diverticulitis at higher cut-off values. This makes high cut-off of WCC and CRP a dependable test to use as a determinant in complicated diverticulitis, and hence, a strong predictor. However, the drawback of high cut-off values of inflammatory markers is reduced sensitivity and a considerable percentage of complicated diverticulitis cases being missed.

One recognized limitation of this study is its small sample size. Even within the small sample size, the results of the study have achieved statistical significance and internal validity was ensured. A larger sample size would have alleviated doubts in generalizability of the study findings. We collected data from consecutive patients in a complicated diverticulitis group over the period of the study and also used consecutive patients for the control group to avoid sampling bias. The findings of the study are probably valid for Western and industrial societies where the prevalence of diverticulitis and complicated diverticulitis is similar to the study population.

Conclusion

Contrary to what has been previously reported in the literature, we found that WCC remains a significant test in diagnosing complicated diverticulitis. A high cut-off value of 18 $\times 10^9$/L is useful in predicting complicated diverticulitis with high positive predictive value. When compared to WCC, CRP is a more sensitive test in detecting complicated diverticulitis. We recognized a cut-off value of 160 mg/L to be a suitable level to determine complicated diverticulitis with a significant positive predictive value.

WCC and CRP are very specific predictors of complicated diverticulitis with high positive predictive values at high cut-off values of 18 $\times 10^9$/L and 160 mg/L, respectively. However, at these high cut-off values the sensitivity of the tests suffers significantly and a considerable portion of complicated diverticulitis will be missed. For that reason, using radiological diagnosis continues to be important part of the assessment of patients with acute diverticulitis.

Both WCC and CRP are very useful predictors of complicated diverticulitis. Further studies can be implemented to formulate a predictive model of complicated diverticulitis, which can be useful in areas where CT scanning availability is limited.

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