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A Weighted ROC Curve Model Identifies Sample Specific Prognostic Indicators for Outcomes in Patients with Acute Severe Ulcerative Colitis

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Overview: Ulcerative Colitis

- A form of inflammatory bowel disease
 - Of which the main types are Crohn's Disease and Ulcerative Colitis
 - Incidence of Ulcerative Colitis is 10-12/100,000 in the US
 - 10-15% of Ulcerative Colitis patients will develop an acute severe attack that will require intensive medical treatment
- An acute attack of ulcerative colitis
 - According to the Truelove and Witts criteria, an acute severe attack of UC is defined by the presence of multiple clinical factors including
 - passage of ≥ 6 bloody stools per day, with one or more of the following:
 - temperature $> 37.5^{\circ}\text{C}$
 - pulse rate $> 90/\text{min}$
 - haemoglobin $< 10.5\text{g/dl}$
 - erythrocyte sedimentation rate (ESR) $> 30\text{mm/hour}$

Project Aims

- Aim 1
 - What clinical factors can be used to determine the need for surgery, both at hospital discharge, and at 12 months?
- Aim 2
 - What factors can be used to predict response to treatment with intravenous steroids?
- Aim 3
 - What methods are currently being used, what clinical factors are being considered, and using data from the Brisbane IBD cohort, can we improve on these?
- Questions
 - Can we build a model to successfully predict need for surgery and response to intravenous steroids?
 - How statistically strong is this model?

Study sample and clinical measures

- Patients presented with a severe episode of ulcerative colitis between 1996 and 2008 and were followed prospectively to evaluate treatment outcomes
- Patients clinical evaluation included
 - daily stool frequency
 - presence or absence of visible blood
 - abdominal tenderness
 - pulse rate, and
 - Temperature
- Clinical measurements included
 - full blood count
 - ESR
 - CRP
 - electrolytes
 - liver function tests, and
 - serum magnesium and cholesterol (for those on Cyclosporin)

Clinically Relevant Outcome

- Defined as either:
 - response to medical therapy, or
 - colectomy at the time of discharge,
 - or colectomy at reassessment 12 months from the discharge date
- Responders were those patients who:
 - achieved a stool frequency of < 4 stools per day without visible blood by day 7.
- Indications for colectomy included:
 - either failure to respond or
 - deterioration during medical treatment as measured by:
 - increasing bloody diarrhoea
 - abdominal pain and tenderness
 - perforation, and/or
 - increasing colonic dilatation

Statistical Analysis

- Focus upon four points:
 - What is the outcome?
 - What are the indicator variables (exposures, clinical features)?
 - What methods can we use to test the need for surgery?
 - How do the current benchmarks compare with newly devised prognostic indicators?

Statistical Analysis: What is the outcome?

- Patient outcome was classified into three groups:
 - response to intravenous steroid treatment (IVR). In this group, responders were those patients who made an adequate response to intravenous steroids alone and hence avoided colectomy, while non-responders were those patients who required either colectomy or salvage therapy with cyclosporine or infliximab, after failing to respond to intravenous steroids
 - need for colectomy prior to discharge
 - need for colectomy within 12 months from time of discharge

Statistical Analysis: Indicator variables

- Clinical characteristics including:
 - Age at diagnosis
 - Maximum disease extent (MDE)
- Clinical measures:
 - Pulse rate
 - Body temperature
 - Haemoglobin level
 - Serum albumin level
 - Bowel movements (day 1 and 3)
 - Erythrocyte sedimentation rate (ESR) (day 1 and 3)
 - C-Reactive Protein (CRP) (day 1 and 3)
- Previous prognostic indicators:
 - Travis
 - Lindgren
 - Seo

Statistical Analysis: Methods

- **Statistical Methods including:**

- Chi Square and Fisher's Exact test
- Survival analyses using Kaplan Meier
- Receiver Operating Characteristic (ROC) analyses including:
 - Area under the curve (95%CI)
 - Sensitivity, Specificity
 - Bootstrapping, performance, accuracy
- Statistical weighting for ROC indicators to account for possible over/under specification in the model. ROC criteria were devised using:
$$\text{Log (1/RF1 p-value)} + \text{Log (1/RF2 p-value)} + \text{Log (1/RF...k p-value)}$$
- Quantitative measures were transformed into binary variables, firstly by using published cut off values, and secondly by using the criteria predicted through individual ROC analyses.

Statistical Analysis: Previous Benchmarks

- Previous studies have used the ROC to define a criterion by which a patient would need surgery. These include:
 - The Travis index uses only CRP and bowel movements at day 3 to devise the need for surgery
 - The Lindgren index uses the same two factors, using a weighted CRP value ($\text{CRP} \times 0.14$)
 - The Seo index uses a weighted quantitative algorithm using presence of bloody stool, bowel movements, erythrocyte sedimentation rate (ESR), haemoglobin level (Hb) and albumin (A) levels
- **Question:**

Can we develop using our own statistical methods, a prognostic indicator that performs as well as the current benchmarks, and, test these upon the response to IV steroids as an endpoint, rather than surgery

Results

Variables	IVS non-responders (n = 52)	IVS responders (n = 37)	Univariate p-value
Maximum disease extent			
Left sided	13	13	
Extensive	39	24	0.3
Disease duration			
< 60 months	25	10	
≥ 60 months	27	27	0.06
Body temperature			
≤ 37.5oC	32	30	
> 37.5oC	20	7	0.05
Haemoglobin level			
< 10.5 g/dL	39	33	
≥ 10.5 g/dL	13	4	0.09
Serum albumin level			
≤ 35 g/L	12	19	
> 35 g/L	40	18	0.006
Erythrocyte sedimentation rate (day 1)			
≤ 30	17	12	
> 30	34	25	0.93
CRP (day 1)			
< 45 mg/L	15	14	
≥ 45 mg/L	37	23	0.37
Bowel movements (day 3)			
< 8	24	31	
≥ 8	28	6	0.0003
Erythrocyte sedimentation rate (day 3)			
≤ 30	21	19	
> 30	30	14	0.14
CRP (day 3)			
< 45 mg/L	27	32	
≥ 45 mg/L	25	5	0.0007

* Note: Some frequencies do not add to total due to some missing data

Results

Variables	Outcome at discharge		Univariate <i>p</i> -value	Outcome at 12 months		Univariate <i>p</i> -value
	No surgery (n = 56)	Surgery (n = 33)		No surgery (n = 48)	Surgery (n = 41)	
Maximum disease extent						
Left sided	21	5		19	7	
Extensive	35	28	0.03	29	34	0.02
Disease duration						
< 60 months	18	16		13	21	
≥ 60 months	37	17	0.14	35	20	0.02
Body temperature						
≤ 37.5oC	40	22		36	26	
> 37.5oC	16	11	0.64	12	15	0.24
Haemoglobin level						
< 10.5 g/dL	47	25		41	31	
≥ 10.5 g/dL	9	8	0.34	7	10	0.24
Serum albumin level						
≤ 35 g/L	24	7		22	9	
> 35 g/L	32	26	0.23	26	32	0.02
Erythrocyte Sedimentation rate (day 1)						
≤ 30	21	8		17	12	
> 30	35	24	0.20	31	28	0.59
CRP (day 1)						
< 45 mg/L	21	8		18	11	
≥ 45 mg/L	35	25	0.05	30	30	0.28
Bowel movements (day 3)						
< 8	39	16		34	20	
≥ 8	17	17	0.04	14	21	0.06
Erythrocyte Sedimentation rate (day 3)						
≤ 30	29	11		25	15	
> 30	22	22	0.06	18	26	0.05
CRP (day 3)						
< 45 mg/L	44	15		38	21	
≥ 45 mg/L	12	18	0.001	10	20	0.005

* Note: Some frequencies do not add to total due to some missing data

Result: Weighted Criterion for the ROC Model

- Data collected were quantitative in nature
- Two methods of binary categorisation:
 - As per published cut off values
 - As per ROC criteria
- If a patient was positive for the clinical measure, that is they have a greater than the expected level for that measure, they were given a 1
- If the patient was allocated a 1, we used the inverse log of the associated p-value from the univariate ROC analysis to transform the 1 into a weighted quantity.
- If a patient had 2, 3, or more 1 values for different measures then their weighted score increased by the inverse log of the associated p-value.

Result: Weighted Criterion for the ROC Model

- Example:

Outcome variable: response to intravenous steroids, for patient A

Risk factor: serum albumin

p-value: 0.0115

weighted value: 4.47

Risk factor: CRP level day 3

p-value: 0.0046

weighted value: 5.38

If patient A had serum albumin of less than or equal to 35, and CRP of greater or equal to 45 then their weighted score would be $4.47 + 5.38$.

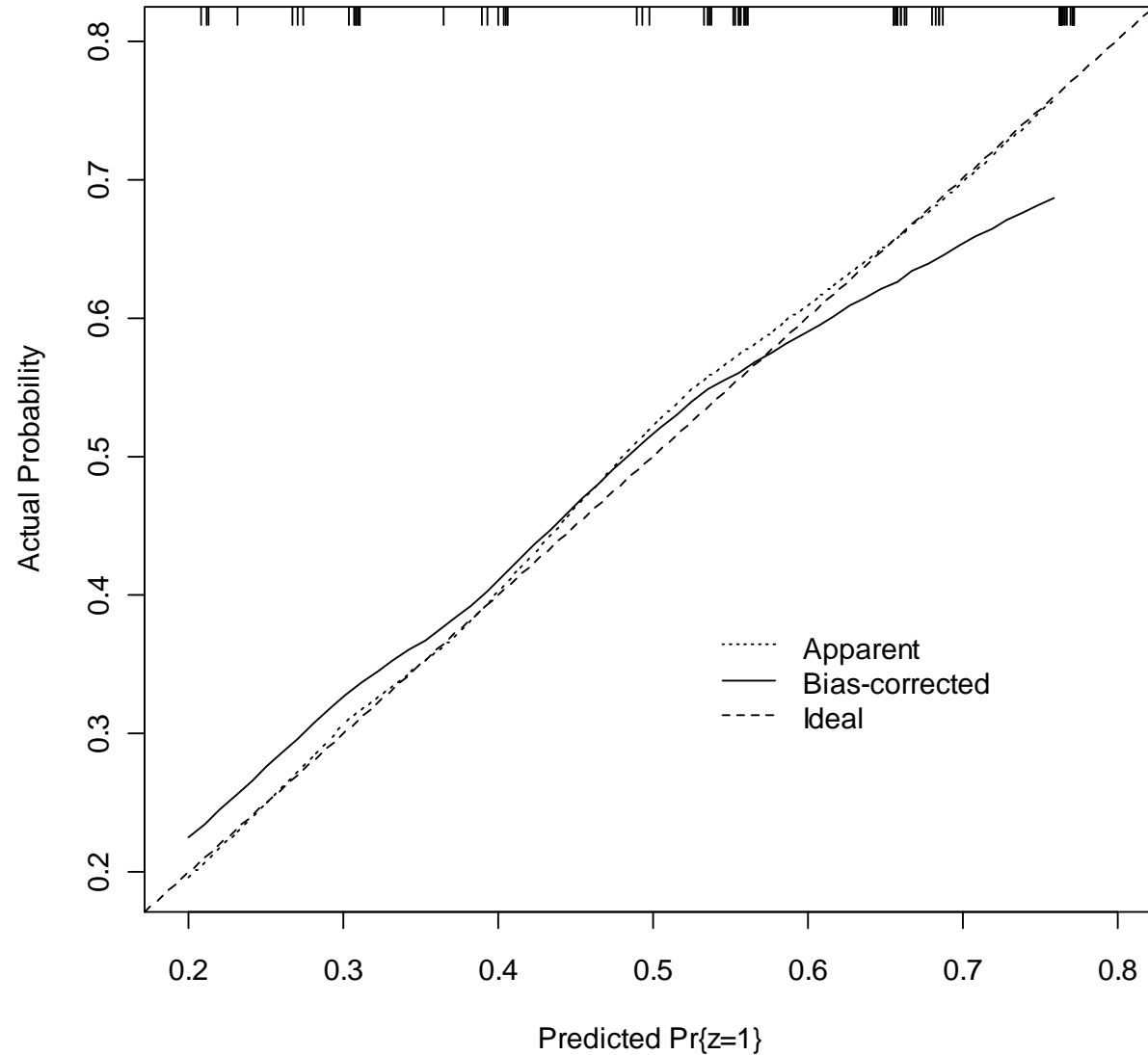
Results

Variable	N (Responder/Non)	Criterion	AUC (95%CI)	p-value	Sensitivity (%)	Specificity (%)
IVR						
Body temperature (day 1)	37/52	≤ 37.2	0.63 (0.52 - 0.73)	0.0315	70.3	53.8
Serum albumin level (day 1)	37/52	> 34.0	0.65 (0.54 - 0.75)	0.0115	62.2	67.3
Bowel movements (day 3)	37/52	≤ 8	0.69 (0.58 - 0.78)	0.0006	91.9	46.2
Erythrocyte sedimentation rate (day 3)	33/51	≤ 51	0.62 (0.51 - 0.73)	0.0467	84.8	43.1
CRP (day 3)	34/52	≤ 46	0.67 (0.56 - 0.76)	0.0046	88.2	48.1
Surgery Discharge						
	N (Surgery/ No Surgery)					
Serum albumin level (day 1)	33/56	≤ 33	0.62 (0.51 - 0.72)	0.0417	66.7	60.7
Erythrocyte sedimentation rate (day 3)	33/51	> 25	0.67 (0.56 - 0.77)	0.0067	78.8	51.0
CRP (day 3)	33/53	> 25	0.67 (0.56 - 0.77)	0.0070	75.8	58.5
Surgery 12 months						
	N (Surgery/ No Surgery)					
Serum albumin level (day 1)	41/48	≤ 35	0.63 (0.52 - 0.73)	0.0253	78.0	45.8
Bowel movements (day 3)	41/48	> 9	0.63 (0.52 - 0.73)	0.0369	36.6	85.4
Erythrocyte sedimentation rate (day 3)	41/43	> 22	0.65 (0.53 - 0.75)	0.0162	78.0	46.5
CRP (day 3)	41/45	> 46	0.63 (0.52 - 0.73)	0.0307	48.8	80.0

Results: Travis, Lindgren & Seo Indices

Variable	N (Responder/Non)	Criterion	AUC (95%CI)	p-value	Sensitivity (%)	Specificity (%)
IVR						
Lindgren	34/52	≤ 12.74	0.76 (0.66 - 0.85)	0.0001	91.2	57.7
Seo	34/51	≤ 223.2	0.61 (0.50 - 0.72)	0.0600	81.1	51
Travis	34/52		0.76 (0.65 - 0.84)	0.0001	82.4	69.2
Surgery Discharge						
	N (Surgery/ No Surgery)					
Lindgren	33/53	> 10.44	0.71 (0.60 - 0.80)	0.0030	81.8	58.5
Seo	32/53	> 218.4	0.58 (0.47 - 0.69)	0.1900	62.5	53.6
Travis	33/53		0.72 (0.62 - 0.81)	0.0002	75.8	67.9
Surgery 12 months						
	N (Surgery/ No Surgery)					
Lindgren	41/45	> 6.96	0.69 (0.58 - 0.79)	0.0010	95.1	42.2
Seo	40/48	> 223.6	0.57 (0.46 - 0.68)	0.2400	42.5	72.9
Travis	41/45		0.69 (0.58 - 0.78)	0.0010	68.3	68.9

Mean absolute error after 1000 bootstrap repetitions, IVR



B= 1000 repetitions, boot

Mean absolute error=0.02058336 n=90

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Thank you

