Title: Development and internal validation of clinical prediction models for relapse and death in patients treated for complicated intra-abdominal infections in the United Kingdom.

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Keywords

Complicated intra-abdominal infections; prediction models; relapse; death;

Abstract

Objectives: Complicated intra-abdominal infections (cIAI) are associated with significant morbidity and mortality. Here we describe the clinical characteristics of patients with cIAIs in the UK, and develop prediction models to help identify patients at increased risk of death or relapse after cIAI treatment.

Methods: A multi-centre observational study was conducted from August 2016 to February 2017. Adult patients diagnosed with cIAI were included. Multivariable logistic regression was performed to develop prediction models for mortality and cIAI relapse. Model discrimination was tested using the c-statistic and model calibration was tested using calibration slopes. The prediction models were then presented as a point score system following internal validation.

Results: In total, 417 patients were included from 31 centres. At 90 days following cIAI diagnosis 17.3% had a cIAI relapse and the mortality rate was 11.3%. Predictors in the final model for mortality were age, cIAI aetiology, perforated viscus and source control procedure. For the model for cIAI relapse predictors included collections, outcome of initial management and antibiotic duration. The c statistic (adjusted for model optimism) was 0.79 and 0.74 for the mortality and cIAI relapse models respectively; adjusted calibration slopes were 0.88 and 0.92 respectively.

Conclusion: We have developed prediction models to identify patients at an increased risk of cIAI relapse or death after treatment, thus informing subsequent management and follow up. These models require external validation before use in clinical practice.

Introduction

Complicated intra-abdominal infections (cIAIs) are defined as intra-abdominal infections that have extended beyond the hollow viscus of origin into the peritoneal space and are associated with either abscess formation or peritonitis.[1] One in five patients with cIAI fail treatment[2, 3] and in high-risk groups such as the elderly and those with severe sepsis, mortality has been reported up to 50 to 80%.[4, 5]

Treatment of cIAIs includes source control and administration of antibiotic therapy. Guidelines recommend that source control procedures should be the least invasive method able to obtain adequate source control, and antibiotics be limited to 4 to 7 days.[6] Despite the current recommended treatment strategies, patients still suffer high rates of relapse and mortality after cIAI treatment. Additional strategies are therefore required to help optimise the care of patients with cIAI. Use of clinical prediction models may be able to optimise the care of patients with cIAI by identifying patients who have the highest risk of cIAI relapse or death. Currently, disease specific prediction models for cIAI exist, which are designed to be used peri-operatively in patients undergoing source control but are rarely used in routine clinical care. These identify patients at the highest risk of death, so the aggressiveness of treatment can be decided early.[4, 7] However, these models are restricted to patients who undergo a source control procedure. Additionally, they do not predict the risk of relapse, one of the most common adverse events after cIAI treatment. We undertook a multicentre observational study to describe the cIAI patient population in the UK and developed clinical prediction models to determine the probability of relapse and death in patients with cIAI, managed with and without source control procedures. To facilitate interpretation and use of the models they have been presented as point score systems.[8] These systems assign values to the identified clinical predictors in order to allow a risk score to be calculated and are designed to be used in the clinical setting.

Methods

A multicentre observational study was performed between August 2016 and February 2017. The study was classed as a service evaluation, registered at participating sites and information governance approval was obtained. Data were collected prospectively and recorded using Microsoft® Excel (Microsoft, Redmond, Washington, USA), and anonymised before centralisation.

Centre eligibility

All hospitals in the UK were eligible to enter patients. Invitations to participate were distributed via trainee-led, surgical and infection research collaboratives.

Patient eligibility

Patients were screened prospectively on inpatient wards, including intensive care units. To reduce bias, investigators were asked, where possible, to recruit consecutively identified eligible patients. Patients were included if they were >18 years old with confirmed cIAIs. Patients were excluded if they had a cIAI diagnosed within the previous year; or their cIAI was diagnosed >7 days prior to screening. Patients were also excluded if they had primary appendicitis managed surgically, active necrotising pancreatitis (not excluding discrete pancreatitis infections e.g. abscess, infected pseudocyst), primary (spontaneous) bacterial peritonitis, and continuous ambulatory peritoneal dialysis peritonitis, as these were considered to be distinct clinical conditions with specific management protocols.

Outcome measures

The major outcomes assessed were the rate of cIAI relapse, and all-cause mortality within 90 days of cIAI diagnosis. These same outcomes were considered when generating the clinical prediction models. Additional outcome measures under investigation included the number of days hospitalised, time to relapse or death, and time to clinical improvement.

Definitions

A diagnosis of cIAI was based on either a) a combination of radiological and clinical features consistent with cIAI including a fluid collection and/or perforated viscus, a temperature of ≥38°C or <35°C degrees and a neutrophil count >7.5 x 10*9/L) or b) intra-operative confirmation of an abscess or perforated abdominal viscus. Additionally, the diagnosis was confirmed by a consultant surgeon.

A cIAI relapse could only occur after source control and/or antibiotic therapy to manage the primary cIAI was considered to have been successful. This would be demonstrated by the cessation of antibiotics and there being no further source control procedures planned. The diagnosis of cIAI relapse was made using the same criteria as a cIAI but could also include probable cIAIs, where, in the absence of radiological imaging no other source was identified and a diagnosis was confirmed by a consultant surgeon as a cIAI relapse.

Change of antibiotic treatment due to clinical failure was defined as a change of antibiotic therapy where the clinician collecting the data had determined failure of the previous antibiotic regimen. Where there was failure of primary treatment of cIAI, the reason was taken as the main factor to which the clinician collecting the data attributed responsibility.
Finally, failure of initial management was defined as requiring an additional unplanned source control procedure and/or a change of antibiotics due to either failure of antibiotics or presence of resistance.

Statistical analysis

Clinical prediction models were developed in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement[9], see supplementary material.

Demographic, clinical and treatment characteristics of patients who died were compared with those who survived; and those who had a cIAI relapse were compared with those who did not

have a cIAI relapse. Categorical data are presented as proportions. Continuous data were tested for normality by visual assessment of the histogram and then summarised as medians and interquartile ranges (IQR). Comparisons were tested using either a Chi-square test (or Fisher exact test if appropriate) for categorical data or the Mann-Whitney U test for continuous skewed variables.

Multivariable logistic regression was used to develop prediction models to determine which characteristics were associated with either death, or with cIAI relapse. Variables included in the pool of potential predictors were identified based on their clinical importance and likelihood to affect outcomes.[4, 10] The variables assessed for potential inclusion in the models for relapse and mortality were: age, gender, underlying pathology, site of cIAI, presence of perforation, presences of collection(s), presence of anastomotic leak and if there was failure of initial management. Treatment variables which comprised of duration of antibiotic therapy and type of source control procedure performed were also included.

Missing data in the dataset, were assumed to be missing at random. Multiple imputation via chained equations was therefore undertaken to account for missing data. A set of 20 imputed datasets was created using predictive mean matching.[11] Functional form for continuous variables was assessed via fractional polynomials within each imputed dataset. Variables were selected for inclusion in the final model within each imputed dataset via backwards selection with a p-value of 0.10. Variables that featured in at least 10 of the 20 imputed models were selected for the final model. Pooled odds ratio and intercepts were calculated according to Rubin's rule.

Apparent measures of model performance were calculated for the final multiply imputed model. Discrimination was evaluated via the c-statistic and calibration was assessed via the expected to observed ratio calibration slope. C-statistics resulting from the imputed dataset were pooled via robust methods and therefore the median of the imputed estimates is

presented.[12, 13] Calibration was also observed via a calibration plot for each imputed dataset separately and the median of the imputed estimates provided.[13]

Non-parametric bootstrapping was used to estimate optimism, and examine model stability. In each of 500 bootstrap samples, the entire modelling process, including predictor selection, was repeated and the apparent model performance (calibration and discrimination in the bootstrap sample) was compared with the performance in the original sample per multiply imputed dataset.

The median optimism across all imputed samples was then used to calculate the optimism-adjusted c-statistic and optimism-adjusted calibration slope.[14] Using the latter as a uniform shrinkage factor, all the predictor effects in the final developed model were penalised in order to account for over-fitting.[15]

The pool of potential predictors for the backwards selection was any predictor in a final multivariable model for each imputed dataset (collection, source control, gender, duration of antibiotics, perforated viscus and failure of initial management).

The resulting optimism adjusted prediction models were then presented as a point score system by assigning integer scores to the coeffcients.[8]

Subgroup analysis was performed to determine if specific microbiological data (when available) were associated with certain clinical outcomes.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and R Core Team, version 3.6.1.

Results

Participant characteristics

Data were collected on a total of 463 patients from 31 hospitals in the UK. In total, 417 patients were included in the final analysis; the data provided did not appear to meet the inclusion criteria in 41 patients and five patients died within 72 hours of diagnosis. Table 1 summarises the demographics and cIAI characteristics of included patients. Out of the 417 patients, 53.7% (224/417) were female and the mean age was 62.5 years (standard deviation [SD] 17.7 years). Diverticular disease and post-operative complications were the most common underlying aetiologies in patients with cIAI, accounting for 32.1% (134/417) and 21.8% (91/417) of cases respectively. The most common site of infection was the colorectum (56.6%, 236/417).

Radiological features of cIAI included perforated viscus (61.9%, 231/373), collections (57.7%, 232/402) and anastomotic leaks (10.1%, 41/406). Of the 232 patients with collections, 75.9% had a single abdominal collection on imaging and 24.1% patients had multiple collections. The median maximum depth of the largest collection present was 6cm (IQR 4.0 to 8.8cm).

Table 1. Demographics and clinical characteristics of patients with cIAI

Variable	Total, n 417 (%)
Gender: Female sex	224/417 (53.7)
Mean (SD) age (years)	62.5 (17.7)
Clinical characteristics	
Site (origin) of cIAI	
Colorectum	236/417 (56.6)
Small bowel	44/417 (10.6)
Gastro-oesophageal	41/417 (9.8)
Biliary	38/417 (9.1)
Other	31/417 (7.4)
Appendix	20/417 (4.8)
Unknown	7/417 (1.7)
Underlying pathology	
Diverticular disease	134/417 (32.1)
Post-operative complications	91/417 (21.8)
Other	77/417 (18.5)
Perforated peptic ulcer	37/417 (8.9)
Cancer	30/417 (7.2)
Inflammatory bowel disease	19/417 (4.6)
Biliary stones and/or cholecystitis	19/417 (4.6)
Appendicitis	10/417 (2.4)
Perforated viscus*	231/373 (61.9)
Collection present•	232/402 (57.7)
Single collection	176/232 (75.9)
Multiple collections	56/232 (24.1)
Median depth of biggest collection, n=213†, cm (IQR)	6.0 (4.0-8.8)
Anastomotic leak°	41/406 (10.1)
Data missing for *44 patients, •15 patients, †19 and °11 patients	

Patient management

Source control procedures: 30.8% (128/416) of patients did not undergo a source control procedure, 14.2% (59/416) had percutaneous radiologically guided drainage and 55.0% (229/416) had a surgical procedure. Surgical resection and proximal diversion was the most frequently performed surgical procedure (44.1%, 101/229). A higher proportion of patients who had surgical source control had a perforated viscus (72.6% compared to 44.4% of patients who had percutaneous drainage and 52.9% of patients who had no source control). Patients undergoing percutaneous drainage were more likely to have a collection (91.4% compared with 42.6% of patients undergoing a surgical procedure and 68.5% of patients who had no source control) (see supplementary material).

Antibiotic treatment: The median duration of antibiotic treatment in this cohort was 12 days (IQR 7 to 18.5 days). Median antibiotic duration exceeded seven days, irrespective of whether or not patients had a source control procedure. The antibiotic duration was a median of 10.9 days (IQR 7-17days) for those who had a surgical procedure, 14 days (IQR 10-24.5 days) for those who had percutaneous drainage only and 12 days (IQR 8.5-19 days) for those who had no source control procedure. Piperacillin-tazobactam and amoxicillin-clavulanic acid were the antibiotics most frequently used in the treatment of cIAI (see supplementary material).

An additional unplanned source control procedure was performed in 54.5% of patients who relapsed compared with 9.8% of patients who did not ($p =< 0.001$). Similarly, a change of antibiotics due to perceived clinical failure was required in 36.5% who relapsed compared with 14.7% of patients who did not ($p = < 0.001$).

Clinical outcomes

Overall, 17.3% (72/417) of patients had a cIAI relapse and 11.3% (47/417) of patients died after 72 hours (total mortality including patients who died within 72 hours of diagnosis 52/422; 12.3%). The median number of days in hospital was 17 days from date of cIAI diagnosis (IQR 9.0-29.0). The commonest reported cause of cIAI relapse was failure of source control (Table

2). The median time to improvement (defined as: apyrexial (<38 °C) for > 24 hours and white cell count <11 x 10^9/L) from date of diagnosis was 7 days (IQR 3 to 14 days). The mortality rate in patients who had a cIAI relapse was 11.1% compared to 10.3% in those who did not have a cIAI relapse (p = 0.837). Median antibiotic treatment duration was longer in patients who survived to day 90, 12 days (IQR 8 to 19) vs 9 days (IQR6 to 14.5 days), p = 0.007. Patients who had a cIAI relapse had longer antibiotic treatment durations for their initial cIAI compared to those who did not relapse (median duration 15 days (IQR 9.75 to 21.25) vs 11 days (IQR 7 to 17), p = 0.001). Median length of hospital stay for primary admission with cIAI was longer in patients who relapsed; 29 days (IQR 15-49 days) compared to 15 days (IQR 8 -25 days), p = < 0.001, in those who did not have a cIAI relapse. Of the patients who had collections associated with their cIAI, the rate of relapse in those with multiple collections was 41.2% (21/51) compared to 19.6% (35/179) of those who has single collections (p = 0.002).

Table 2. Outcomes in patients with cIAI

Outcome (n=number of patients)	No. (%)
cIAI relapse*†	72/417 (17.3)
Death (all cause)*	47/417 (11.3)
Aetiology of relapses (n =72)	
Failure of source control	44/72 (61.1)
Failure of antibiotic treatment	7/72 (9.7)
Unknown/Other	21/72 (29.2)
Time till relapse of cIAI (n=70)^, Median (IQR)	18.0 days (12.8-30.3)
Time till death from diagnosis of cIAI (n=40) Median (IQR)**	23.0 days (12.0-51.0)
Days to improvement (n=295) °, Median (IQR)	7.0 days (3.0 -14.0)
Days hospitalisation within 90 days (n=401)°°, Median (IQR)	17.0 days (9.0-29.0)
* Within 90 days of cIAI diagnosis. †data regarding cIAI relapse missing or unknown in 5 patients. Data missing for ^2, **7, °122 , °° 16 patients	

Model development and model performance measures

Results for the univariable modelling of both outcomes are presented in the supplementary material.

Following internal validation and imputation, the models showed good performance. The model c statistic was 0.82 (0.77, 0.88) for the model predicting mortality and 0.78 (0.72, 0.84) for the model predicting relapse. These were 0.79 and 0.74 respectively after adjusting for model optimism. The calibration plots for relapse and mortality can be found in the supplementary material and show good agreement between observed and predicted probabilities for both models. The calibration slopes (adjusted for model optimism) were 0.88 and 0.92 respectively

For mortality, the predictors included in the parsimonious multivariable logistic regression model were age, cIAI due to cancer, type of source control procedure performed and the presence of a perforated viscus.

Table 3: Multivariable models for risk of mortality adjusted for shrinkage

Predictor	Comparison	Mortality, OR* (95% CI)
Intercept, log odds ratio (SE)		-7.53 (1.10)
Underlying pathology	Diverticular disease	1.00
	Cancer	4.07 (1.58, 10.48)
	Post-op complication	1.30 (0.46, 3.68)
	Other	2.04 (0.98, 4.21)
Source Control	Surgical	1.00
	Radiological drainage	0.33 (0.08, 1.30)
	No source control	1.58 (0.81, 3.09)
Age (years)	23.5-34.5	1.00
	34.5-55.5	2.80 (1.91, 4.12)
	55.5-65.5	7.61 (3.57, 16.22)
	65.5-75.5	14.49 (5.34, 39.29)
	75.5-85.5	27.59 (8.00, 95.17)
	85.5-95.5	52.54 (11.98, 230.49)
Perforated Viscus	Not present	1.00
	Present	2.40 (0.94, 6.11)

*Adjusted for shrinkage based on the median optimism-adjusted calibration slope

Predictors included in the model for cIAI relapse were presence of a collection, antibiotic duration and whether or not there was failure of initial treatment (defined as 'requiring an additional unplanned source control procedure or a change of antibiotics due to either failure of antibiotics or presence of resistance').

Table 4. Multivariable models for risk of relapse adjusted for shrinkage

Predictor	Comparison	Relapse, Adjusted OR* (95% CI)
Intercept, log odds ratio (SE)		-2.30 (0.35)
Collections	Not present	1.00
	Present	1.72 (0.93, 3.17)
Duration of antibiotics	< 5 days	1.00
	5-7 days	4.71 (0.90, 24.59)
	8-11 days	6.82 (0.88, 52.85)
	12-17 days	7.86 (0.87, 70.85)
	18-41 days	8.65 (0.87, 86.37)
	> 41 days	8.87 (0.86, 91.07)
Failure of initial management	Not present	1.00
	Present	5.27 (2.96, 9.40)

*Adjusted for shrinkage based on the median optimism-adjusted calibration slope

The clinical prediction models have been presented using a point score system (Tables 5 and 6). The point score system for mortality providing predicated probabilities between 3% to 71% and the scoring system for cIAI relapse between <4.13% to 52.43%.

Table 5a. Points score system for probability of death after cIAI treatment

Points	
Age (years)	
< 34.5	-3
34.5-55.5	-2
55.5-65.5	0
65.5-75.5	1
75.5-85.5	2
> 85.5	3
Perforated viscus	1
Type of source control performed	
Percutaneous drainage	-2
Surgical source control	0
No source control	1
Aetiology of cIAI	
Cancer	2
Diverticular disease	0
Post-operative complication	0
Other	1

Table 5b.Estimate of risk based on score for mortality

Score	Estimate of risk of death after cIAI treatment
≤ 0	3%
1	5%
2	9%
3	15%
4	26%
5	40%
6	56%
7	71%

Table 6a. Points score system for probability of cIAI relapse after cIAI treatment

Predictor	Points
Treatment failure *	3
Collection(s) present	1
Antibiotic duration	
< 5 days	-6
5 – 7days	-1
8 -41 days	0
> 41 days	1

*** defined as requiring an additional unplanned source control procedure or a change of antibiotics due to either failure of antibiotics or presence of resistance.**

Table 6b. Estimate of risk for cIAI relapse after cIAI treatment based on score

Score	Estimate of risk for cIAI relapse after cIAI treatment
< 1	< 4%
0	7%
1	11%
2	18%
3	27%
4	39%
5	52%

Subgroup analysis

Sub-group analysis of patients who had samples sent for microbiological culture found that 58/273 (21%) patients had samples that grew antibiotic resistant organisms (amoxicillin-

clavulanic acid/ piperacillin-tazobactam resistant/ ciprofloxacin resistant Enterobacteriaceae, Amp C or ESBL producers, vancomycin resistant enterococci and/or methicillin resistant *Staphylococcus aureus*). Organism data were missing in 13 patients. Patients who had antibiotic resistant bacteria isolated from their clinical samples had increased rates of cIAI relapse (33.3% vs 19.3%, p value 0.031), longer antibiotic treatment durations (median duration 16.5 days [IQR 10 to 29] vs 13 days [IQR 7 to 19], p 0.003) and longer hospital stays (median length of hospitalisation following cIAI diagnosis 26.5 days [IQR 14.75 to 42.25] vs 15 days [IQR 9 to 30], p < 0.001). The presence of resistant organisms was not associated with mortality (17.9% in those who died vs 22.8% in survivors, p 0.55).

Discussion

To the best of our knowledge this is the largest study describing the clinical characteristics and management strategies of cIAIs in the United Kingdom. We used the data collected from this large UK cohort to develop prediction models for cIAI relapse or death in patients who have been treated for cIAI. We have presented our model using a points scoring system. The probability of death based on our scoring system for predicting the risk of death after treatment ranges from 3% to 71% and the probability of a cIAI relapse ranged from <4 % to 52 % based on the scoring system for risk of cIAI relapse. These values allow clear differentiation between patients' risks of relapse, and/or mortality, so our have potential clinical utility with regard to patient management decisions. They use routinely collected clinical data and so are able to be used readily in standard clinical practice. Our model performance tests indicate that both models have good model performance according to discrimination and calibration tests.

Prognostic scores for complicated intra-abdominal infections already exist, however these are primarily used to predict mortality. The Manheim Peritonitis Index (MPI) is a disease-specific severity score that has been previously established to be an effective prognostic marker in patients with peritonitis[7]. It is a simple tool to use and calculates risk of death based on age, gender, presence of organ failure, presence of malignancy, the duration of peritonitis, origin

of infection and type of exudate identified intra-operatively. The use of operative findings in this score, means it is unsuitable for the 30% of patients with cIAI who do not undergo any source control procedure. In 2015, the World Society of Emergency surgery (WSES) validated a sepsis severity score for patients with intra-abdominal infections. They conducted a prospective multicentre observational study and found that the severity score was useful in predicting survival (mortality 0.63% if score 0-3 and 41.7% if score >7)[4]. This model includes sepsis severity, origin of cIAI, setting of cIAI acquisition, immunosuppression, age and time to source control as predictors. Model performance measures were not reported. These models are generally applied in research studies rather than in clinically.

In our study, our observed rate of cIAI relapse was 17.3%, consistent with the 14-23% reported by others[2, 3]. The predictors we have identified for cIAI relapse and those for mortality are different, with the predictors for mortality largely comprising of non-modifiable risks.

We found that cIAI relapse was not associated with significantly increased mortality, however it was associated with antimicrobial resistance (AMR), longer antibiotic durations and increased length of hospital stays.

In our cohort, 7.7% of patients had an ESBL or Amp-C producing organism isolated, similar to figures reported in a European cohort.[16] AMR was associated with a near doubling of the rate of relapse, from 19.3% to 33%. This highlights that ongoing monitoring for the presence of antimicrobial resistant bacterial infections should be considered important in optimising the care of patients with cIAI.

We recognise several limitations to our study. Firstly, the number of outcome events was small and this restricted the number of variables included in the pool of potential predictors for the multivariable logistic regression model. Secondly, data for several variables were missing, however we carried out multiple imputation to mitigate for this. Thirdly, data were collected at a local level and the validity of the data provided was not audited. Fourthly, some relevant clinical data e.g. severity of sepsis, placement of drains and duration of drainage was not

collected. In our study, we did not remove the patients who died in the no relapse group from our analysis when developing the relapse model. However, there were near equal proportions of patients who had died in the group of patients who had a relapse and those who did not and so we feel that our interpretation of the results is appropriate. Finally, although point score systems facilitate the use of prediction models, they are only able to provide approximate predictions of risk compared to the full models and so are less accurate.[9] However, the clinical predictors selected to be included in the final models are consistent with those described in the literature.

The presented prediction models and subsequent score systems have advantages over existing ones because they provide information on both the risk of cIAI relapse and mortality. In our scoring systems, clinical data collected at the point at which management of the cIAI has been completed are used to predict outcomes at the end of treatment for cIAI. Therefore they can guide decisions on patient follow-up or the need for further intervention at a clinically relevant time. They are simple to use and based on easily accessible patient data. Furthermore, they can be used in all patients who have cIAIs, irrespective of whether or not they undergo source control procedures. These models will now require external validation prior to clinical utility assessment.

Conclusion

With these data we have developed clinical prediction models for cIAI relapse and mortality in patients with cIAIs. Our prediction models have been presented as scoring systems and have the potential to enable early identification of patients at increased risk of cIAI relapse or death. This may change patient management strategies and improve patient outcomes. External validation of these clinical prediction models are required, as are clinical utility studies.

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