Diagnosis of intra-abdominal infections and management of catastrophic outcomes
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External validation of a decision tool to guide postoperative management of patients operated for secondary peritonitis

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Submitted
ABSTRACT

Background
Timely and correct identification of patients in need of an intervention for ongoing abdominal sepsis after initial surgical management of secondary peritonitis is vital but complex. Aim of this study was to externally validate a previously developed decision tool and to evaluate its potential to guide postoperative management.

Method
Prospective observational cohort study including consecutive adult patients undergoing surgery for secondary peritonitis in a single university-based hospital. Assessments with use of the decision tool, based on one intraoperative and five postoperative variables, were performed at least on the second and third postoperative day and when the patients’ clinical status deteriorated. Scores were compared to the clinical reference standard of ongoing sepsis based on the clinical course or findings of imaging or surgery. Additionally, the potential of the decision tool to guide management in terms of diagnostic imaging in three previously defined score-categories (low, intermediate and high) was evaluated.

Results
A total of 161 assessments were performed in 69 patients operated for secondary peritonitis. The majority of cases of secondary peritonitis (68 per cent) were caused by perforation of the gastrointestinal tract. Postoperative ongoing sepsis occurred in 28 patients. The discriminative capacity of the decision tool score was fair (AUC of the ROC of 0.79). Performances on day 2 (AUC 0.93; 95 per cent confidence interval (CI) 0.84 to 1.00) and day 3 (AUC 0.99; 95 per cent CI 0.95 to 1.00) were better than on day 4 to 10 (AUC 0.73; 95 per cent CI 0.62 to 0.85). Good calibration was observed (Hosmer-Lemeshow p=0.20). The incidence rate differed significantly between the three score categories (p<0.001). The negative predictive value of a decision tool score categorized as low probability of ongoing sepsis was 89 per cent (95 per cent CI 82 to 94) and 65 per cent (95 per cent CI 47 to 79) for an intermediate score. Diagnostic imaging was more frequently performed following an intermediate score than following scores categorized as ‘low’ (46 per cent versus 24 per cent; p<0.001).

Conclusion
In patients operated for secondary peritonitis, the decision tool score predicts with fair accuracy whether or not ongoing sepsis is present. In clinical practice a low score has a good negative predictive value for ongoing sepsis.
INTRODUCTION

Secondary peritonitis is caused by a breach in the integrity of the gastrointestinal tract, either by perforation, infection, inflammation or ischaemia. Despite diversity in specific underlying diseases, management of patients with secondary peritonitis is based on several general treatment principles. Achieving adequate source control is one of the most important initial aspects, and for most patients this entails surgical intervention. After the initial surgical procedure, persisting or new-onset abdominal sepsis may necessitate reintervention in up to 34 per cent of patients. It has been well recognized that timely identification substantially contributes to improved survival. Planned reoperations were therefore historically performed to avoid delay in detection. However, during the last decades a more conservative ‘on-demand’ approach, with reoperations performed only in selected patients with clinical deterioration, has been shown to be superior in terms of patient related outcomes and direct medical costs.

Essential to the on-demand strategy mentioned above is vigilant observation during the postoperative course with round-the-clock monitoring and decision-making. The decision to perform a re-intervention is not straightforward. No well-defined and objective criteria exist for something that we call ‘clinical assessment’ in daily practice. Available widely-used intensive care unit (ICU) scoring systems have limited value for the identification of patients with ongoing infection after the initial emergency laparotomy. Although computed tomography (CT) is an important and useful diagnostic for abdominal sepsis, several drawbacks warrant selective usage. Indeed, CT necessitates transfer of a potentially unstable patient from the ICU, the needed administration of contrast agents may induce or aggravate renal injury, and CT entails concerns regarding cost-effectiveness of unclear selection criteria for imaging.

In an attempt to improve postoperative management of patients operated for secondary peritonitis, our study group previously developed and internally validated a prediction model. The model included one intraoperative variable (extent of the contamination during initial surgery) and five postoperative variables (heart rate, haemoglobin level, body temperature, defecation, and the need for administration of inotropic agents) and predicted the probability of ongoing sepsis from an infectious abdominal focus. The prediction model was subsequently translated into a decision tool to guide patient management in terms of diagnostic imaging for three score-based categories. The aim of the current study was to externally validate this decision tool in a new cohort of patients with secondary peritonitis and to evaluate its potential to guide and improve postoperative management.
METHODS

This manuscript was written according to the items for external validation of a prediction model as proposed in the ‘Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD)’ statement. The ethical committee of the Academic Medical Centre approved the study protocol and waived the need for informed consent.

Study design and data collection

Consecutive adult patients (≥ 18 years of age) undergoing emergency surgery (laparotomy or laparoscopy) for secondary peritonitis between January 2014 and March 2015 in a single centre were prospectively included. Secondary peritonitis was defined as an intra-abdominal infection, verified during surgery, caused by perforation or infection of a visceral organ, ischemia or necrosis of part of the gastrointestinal tract, or a postoperative peritoneal infection due to an anastomotic leakage.

Data on patient demographics, aetiology of peritonitis (perforation, ischemia/necrosis or postoperative anastomotic leakage), severity of peritonitis (preoperative APACHE II score and extent of peritonitis during the index operation) and surgical details (surgical approach, whether or not source control was achieved and the employment of a planned relaparotomy strategy) were collected. Furthermore, data on the postoperative course was collected including the use of diagnostic imaging, number of performed radiological and surgical interventions, length of postoperative hospital stay, and in-hospital mortality.

Decision tool assessments

The development of the decision tool has been described elsewhere. In short, the decision tool is composed of six items; heart rate (≤90 bpm / >90 bpm), haemoglobin level (≤5.0 mmol/L / >5.0 mmol/L), body temperature (≤35.5°C or >39°C / >35.5 and ≤39.0°C), defecation (yes / no), extent of contamination found at the index operation (diffuse / local), and the need for administration of inotropic agents (yes / no). With use of a nomogram, depicted in Appendix 1, a probability score can be calculated. For each item points can be obtained with a maximum possible score of 60 points, with a higher score being associated with a higher probability of ongoing sepsis. Three separate categories were previously formulated during development; low probability (0-19 points), intermediate probability (20-40 points) and high probability (more than 40 points). Given the design of the decision tool, patients can be evaluated with the decision tool more than once during a single postoperative period.

With use of the decision tool a score was calculated for each patient (except early deaths after the index operation) on the second and third postoperative day (POD). Furthermore, a score was calculated on every postoperative day within a 10-day period after surgery when
the clinical status of the patient deteriorated and/or led the treating physicians to consider performing diagnostic imaging or re-interventions.

Outcomes

The diagnostic accuracy of the decision tool was calculated by comparing the calculated score with the clinical reference outcome, i.e. ongoing sepsis from an abdominal focus (within 24 hours after the decision tool assessment). Positives were patients who had positive findings of an infectious abdominal focus at relaparotomy, relaparoscopy or diagnostic imaging. Patients who died from presumable ongoing sepsis within 24 hours of the assessment were also considered positives. Negatives were patients with negative findings at reoperation or imaging, and patients with an uncomplicated postoperative course the first 24 hours following the decision tool assessment.

Secondary outcome was the potential of the decision rule to improve patient management in terms of selection for diagnostic imaging on suspicion of an abdominal infectious focus, by comparing the number of imaging studies as advised by the decision tool with the actual number of performed imaging studies.

Statistical analysis

If a patient had an episode of abdominal sepsis, all subsequent decision tool assessments were censored from the analyses of diagnostic accuracy and impact on management. For every assessment using the decision tool, a predicted probability of ongoing sepsis was calculated using the full original model. Subsequently, the full model was updated by re-calibrating the intercept. The discriminative capacity of the updated model was evaluated by calculating the area under the receiving operator characteristics (ROC) curve (AUC) with corresponding 95 per cent confidence intervals (CI). In a ROC curve the diagnostic accuracy of a test is depicted by plotting the sensitivity against 1 – specificity. A perfect diagnostic test with 100 per cent sensitivity and 100 per cent specificity will have its coordinates in the upper left corner resulting in an AUC of 1. Calibration of the updated model was assessed with use of the Hosmer-Lemeshow (H-L) goodness-of-fit test. With this test, assessments were grouped by decile of predicted probability of ongoing sepsis, and the expected number of cases (ongoing sepsis) was compared with the observed number in the ten groups with a Chi² test. A p value > 0.05 indicates good performance.

The calculated scores using the decision tool were categorized into one of the three predefined original categories ('low', ‘intermediate’ and ‘high’). For the ‘low’ and ‘intermediate’ categories, the negative predictive value (NPV) was evaluated by calculating the probability
Chapter 7

of not having ongoing sepsis associated with a score classified as ‘low’ and ‘intermediate’, respectively. For the scores in the ‘high’ category, the probability of ongoing sepsis was calculated (i.e. positive predictive value or PPV).

Normally distributed data were expressed as mean (standard deviation or SD), non-normally disturbed data as median (interquartile range or IQR). All statistical analyses were performed with SPSS® software version 20.0 (IBM, Armonk, New York). P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 72 adult patients with intraoperatively proven secondary peritonitis underwent surgical intervention during the study period. Three patients died shortly after the index operation (within 24 hours) and were thus excluded from analysis. The remaining 69 patients were included (Table 1). The median age of the included patients was 56 years (IQR 36-65), 49 per cent were men, and the median Acute Physiology and Chronic Health Evaluation (APACHE) II score was 11 (IQR 5-13). The most common cause of peritonitis was perforation of a visceral organ (68 per cent) followed by ischemia or necrosis of part of the gastrointestinal tract (17 per cent). A laparoscopic procedure was performed in more than half of all patients (36 of 69; 52 per cent). Thirteen of the included patients died postoperatively, resulting in an in-hospital mortality of 15 per cent (10 of 69), 18 per cent when including the early deaths (13 of 72). The median length of postoperative hospital stay of the surviving patients was 13 days (IQR 6-22).

Outcomes

An abdominal focus for ongoing sepsis was diagnosed 32 times in 28 of 69 patients, with 4 patients having two separate episodes of ongoing abdominal sepsis. With respect to the reference standard: the majority of these episodes of abdominal sepsis were diagnosed on imaging studies (21 of 32; 66 per cent), four episodes were diagnosed on imaging studies with subsequent positive findings at reoperation (4 of 32; 13 per cent), three episodes were confirmed intraoperatively without previous imaging (3 of 32; 9 per cent), and four patients died within a 10-day period after surgery from presumable ongoing abdominal sepsis (4 of 32; 13 per cent).

A total of 53 diagnostic imaging studies were performed in 37 of 69 patients postoperatively (47 CT-scans, 5 ultrasounds and 1 MRI), with a median number of 1 imaging study per included patient (range 0-4 imaging studies). Positive findings on imaging suggestive of an abdominal focus for ongoing sepsis were found in 25 of the 53 imaging studies (47 per cent)
and in 22 of 69 patients. Eighteen patients underwent 21 percutaneous interventions. Eleven reoperations were performed in ten of 69 patients. Four of these reoperations concerned planned relaparotomies; all performed as second look operation for intestinal ischemia, with positive findings in one. The 7 other reoperations were performed in 6 patients and were indicated by the suspicion of ongoing abdominal sepsis with a previous CT in 4 patients; all 7 relaparotomies with positive findings.
Figure 1 Receiver operating characteristics (ROC) curve showing the sensitivity plotted against 1-specificity of the decision tool score in present cohort of patients operated for secondary peritonitis. The area under this ROC curve was 0.79 (95% CI 0.70-0.87).

Table 3 Incidence of ongoing sepsis, diagnostic imaging and reoperations categorized per decision tool score category

<table>
<thead>
<tr>
<th>Category (points)</th>
<th>n</th>
<th>Actual ongoing abdominal sepsis</th>
<th>Diagnostic imaging performed</th>
<th>Reoperation performed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
</tr>
<tr>
<td>Low (0-19 points)</td>
<td>121</td>
<td>108 (89%)</td>
<td>13 (11%)</td>
<td>29</td>
</tr>
<tr>
<td>Intermediate (20-40 points)</td>
<td>37</td>
<td>24 (65%)</td>
<td>13 (35%)</td>
<td>17</td>
</tr>
<tr>
<td>High (41-60 points)</td>
<td>3</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
<td>3</td>
</tr>
<tr>
<td>Total†</td>
<td>161</td>
<td>133 (83%)</td>
<td>28 (17%)</td>
<td>49</td>
</tr>
</tbody>
</table>

†Excluding planned reoperations

Numbers of performed diagnostic imaging studies and reoperations differ from Table 1 as patients were censored from the analyses after an episode of abdominal sepsis had occurred.
Diagnostic accuracy of the decision tool

A total of 161 assessments using the decision tool were performed, with a median number of 2 (IQR 1-2) assessments per patients (Table 2). Of all assessments, 57 (35 per cent) were indicated by the clinical status of the patient. Using the original developed model, the probability of ongoing sepsis for every decision tool assessment was calculated in the present cohort and the model was updated by re-calibrating the intercept (Appendix B). The discriminative capacity of the updated model expressed as the area under the receiving operator curve was 0.79 (95 per cent CI 0.70 to 0.87), suggesting fair discriminatory capacity (see Fig. 1). This AUC was comparable with the discriminative capacity found in the original development cohort (AUC of 0.80; 95 per cent CI 0.69 to 0.82). Assessment of calibration with use of the Hosmer-Lemeshow test showed adequate goodness-of-fit (p=0.20).

A total of 32 assessments were performed on POD2 with 5 cases of ongoing sepsis. The AUC of the assessments on POD 2 was 0.93 (95 per cent CI 0.84 to 1.00). Forty-one assessments performed on POD 3, with only one case of ongoing sepsis, resulted in an AUC of 0.99 (95 per cent CI 0.95 to 1.00). The remaining 88 assessments were performed on POD 4 to POD 10 with 22 cases of ongoing abdominal sepsis. The AUC of these assessments was 0.73 (95 per cent CI 0.62 to 0.85).

The median calculated score was 10 (IQR 6-19) of maximum 60 points. The majority of the decision tool scores were categorized as low probability (0-19 points) of ongoing sepsis (121 of 161; 75 per cent). A score in the intermediate category (20-40 points) was found in 23 per cent of the assessments (37 of 161), while only 3 assessments (2 per cent) resulted a score of 41 points or more (high probability of ongoing sepsis). The actual incidence of ongoing abdominal sepsis per probability score category is shown in Table 3. The incidence rate differed significantly between the three categories (p<0.001). The negative predictive value of a decision tool score categorized as low probability of ongoing sepsis was 89 per cent (95 per cent CI 82 to 94), and 65 per cent (95 per cent CI 47 to 79) for an intermediate score. The positive predictive value of a score in the high category was 67 per cent (95 per cent CI 12 to 95) since 2 of 3 patients with a high score had ongoing abdominal sepsis.

Of all 161 assessments, 92 concerned repeated assessments following a previous assessment. Seventy-three of these 92 repeated assessments resulted in a low score. The negative predictive value of low scores following a previous low score (10 positives of 57 assessments) was comparable to low scores following an intermediate score (3 positives of 13 assessments); 83 per cent (95 per cent CI 67 to 91) versus 81 per cent (95 per cent CI 54 to 95) (p=0.911). For an intermediate score, the positive predictive value (probability of ongoing sepsis) was greater if the assessment succeeded a low score (i.e., an increasing score) compared with an intermediate score (50 per cent; 95 per cent CI 20 to 80, versus 22 per cent; 95 per cent CI 4 to 60), although not statistically significant (p=0.210).
Potential impact of decision tool on postoperative management

Management decisions with respect to postoperative diagnostic imaging (in majority followed by percutaneous drainage) and surgical interventions categorized per decision tool score category are displayed in Table 3. Following 121 decision tool scores in the low category diagnostic imaging still was performed in 29 instances, which diagnosed an abdominal focus in 13 instances (108 of 121 or 89 per cent true negatives of management decisions by the decision tool). If the advice of the decision tool for to the low category would have been adhered (‘no indication for diagnostic imaging’), 16 ‘unnecessary’ imaging studies would therefore have been avoided at the cost of 13 wrongfully omitted studies (missed cases of ongoing abdominal sepsis), while reducing the overall number of performed imaging studies in the total cohort by 59 per cent (29 of 49 imaging studies).

The advice for a patient with an ‘intermediate’ score was to consider imaging. Following 37 ‘intermediate’ scores 17 imaging studies were performed (46 per cent), which were positive for an infectious abdominal focus in 7 instances (7 of 37 or 20 per cent true positives of management decisions of the decision tool). Diagnostic imaging was more frequently performed following an intermediate score than following scores categorized as ‘low’ (46 versus 24 per cent; \( p<0.001 \)). This is in line with the advice of the decision tool corresponding to the intermediate category (‘consider imaging’). Although more imaging studies were performed following an ‘intermediate’ score than following a ‘low’ score, the proportion of ‘justly’ imaging studies (i.e. imaging studies with positive findings) was comparable (45 versus 41 per cent; \( p=0.806 \)).

All scores in the ‘high’ category were followed by imaging, in line with the corresponding advice of the decision tool, and two of three imaging studies were positive for an infectious abdominal focus.

DISCUSSION

In this study a decision tool developed to predict the probability of ongoing abdominal sepsis in patients operated for secondary peritonitis and guide postoperative management was externally validated. The decision tool scores showed good calibration and fair discriminative capacity in the new cohort. The performance was comparable to that found in internal validation, supporting the external validity of the decision tool. Furthermore, the tool had a good negative predictive value of a score categorized as ‘low’ (i.e. probability of not having ongoing sepsis) of 89 per cent, while the positive predictive value (i.e. probability of having ongoing sepsis) of a score categorized as ‘high’ was moderate (65 per cent). Given the design of the decision tool, assessments can be done multiple times during the postoperative course. The found results
Validation of scoring system to aid decision making after surgery for peritonitis

showed that irrespective of previous assessments, low scores preserved their negative predictive value. Furthermore, although not statistically significant, an intermediate score succeeding a low score indicated a greater probability of ongoing sepsis than a constant intermediate score, illustrating that the scores adequately reflected a change in clinical condition. The potential of the decision model to guide postoperative decision making in terms of performing diagnostic imaging was moderate to good. Regarding low scores, ongoing sepsis was present in 11 per cent while omitting diagnostic imaging in these score category would have reduced the number of performed imaging studies in the total cohort by 59 per cent. The advice to perform imaging following a high score did seem accurate, although only very few assessments resulted in a score categorized as high. The strength of the decision tool lies in its negative predictive value for ongoing peritonitis.

Despite progress in the initial surgical management of secondary peritonitis, persisting or new-onset abdominal sepsis by an infectious focus during the postoperative course continues to be a problem. Timely and adequate reintervention is important, but repeated and unnecessary surgical interventions involve additional risks and do not improve outcome. Because of this dilemma, clinical predictors enabling early and correct diagnosis of ongoing sepsis are of great interests. There is no consensus among surgeons which variables are most import during postoperative decision making in patients with peritonitis. Multiple widely-used scores such as the APACHE II score and the Sepsis-related Organ Failure Assessment (SOFA) score have been shown to predict mortality in critically ill patients. However, when evaluating their ability to predict the necessity of surgical reintervention in patients with secondary peritonitis they perform significantly worse. Long ago a prediction model specifically designed to identify patients in need of surgical reintervention has been described (Abdominal Reoperation Predictive Index), but the ARPI score has several limitations which have been previously addressed. Multiple clinical variables are described as predictor of the necessity of a relaparotomy as well, including patient and peritonitis characteristics, surgical variables, and clinical and laboratory variables. Several other markers and variables have also been related to recurrent or ongoing sepsis in patients with peritonitis, such as the serum procalcitonin ratio, increased intra-abdominal pressure and assessments done using intraperitoneal microdialysis. However, these markers lack evaluation of their diagnostic performance and external validation, and not all are widely available. More commonly used diagnostic markers of infectious processes are white blood cell (WBC) count and C-reactive protein (CRP) level. During the development of the current decision tool, these markers failed to show adequate association and were dropped. As these inflammatory markers are already markedly increased in patients with secondary peritonitis in need of surgery, they are less likely to be informative during the postoperative course.
The diagnostic performance of present decision tool was not good enough to completely abstain from clinical judgment. It is not likely that any single marker or decision tool can replace clinical decision-making by the treating multidisciplinary team taking care of the critically ill patient. Useful tools should merely function as aid and may help quantify the possible subjective feeling within the team. The currently studied decision tool therefore incorporates advice regarding postoperative management, aimed to guide the use of diagnostic imaging. The number of missed cases of ongoing sepsis by use of the decision tool may not be low enough for clinical practice and in need of improvement, preferably by integrating the tool in the team’s clinical judgement. The potential of the decision tool to influence the number of ‘unnecessary’ reoperations (i.e. negative findings) could not be assessed in our study, since only few patients underwent a reoperation. This low number of reoperations reflects current clinical practice with on-demand relaparotomy and increased use of percutaneous drainage. The on-demand strategy has become standard for most patients, and progress in imaging techniques, in particular computed tomography, and the introduction of image-guided percutaneous interventions has substituted some reoperations. Furthermore, as CT imaging is now widely used and almost always precedes reintervention, a decision tool should be aimed at triage of diagnostic imaging rather than the decision to perform a surgical intervention.

Some limitations of our study need to be addressed. First, the number of positive cases in our study (ongoing abdominal sepsis) was limited. A larger number of positive cases would have enable more accurate analyses of the positive predictive value. Therefore, no firm conclusion could be drawn regarding this category. Another limitation is the risk of verification bias given our study design. A positive reference standard test was defined as positive findings at imaging or reoperation. Not all patients received the same reference test since not all patients underwent postoperative imaging or a reoperation. Theoretically, patients with an infectious abdominal focus for ongoing peritonitis who did not undergo imaging or a reoperation could therefore have been missed as ‘positives’. However, in clinical practice such patients would probably deteriorate with imaging likely being performed.

Vital to the current standard reoperation on-demand approach in patients operated for secondary peritonitis is vigilant monitoring, with round-the-clock decision-making. To aid this complex process a decision tool has been developed and in the current study externally validated. In patients operated for secondary peritonitis, the decision tool score predicts with fair accuracy whether or not ongoing sepsis is present. In clinical practice a low score of the decision tool has a good negative predictive value for ongoing sepsis. As imaging has become standard and almost always precedes reinterventions, the step-up-approach of clinical suspicion-imaging-reintervention with efficient use of diagnostic imaging without impeding timely diagnosis can be facilitated by the decision tool.
REFERENCES


**Appendix 1** Nomogram depicting the decision tool to predict ongoing abdominal sepsis with advice regarding monitoring and performing imaging studies

<table>
<thead>
<tr>
<th>Category</th>
<th>Decision rule</th>
<th>Computed Tomography</th>
<th>Repeat decision rule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No</td>
<td>No</td>
<td>After 24 hours</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Consider</td>
<td>Consider</td>
<td>After 12 hours</td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td>Yes</td>
<td>After 12 hours if CT is negative</td>
</tr>
</tbody>
</table>

**Appendix 2** Full model on which the decision tool is based enabling calculation of the probability of ongoing sepsis

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contamination (Diffuse)</td>
<td>0.76695</td>
</tr>
<tr>
<td>Defaecation (No)</td>
<td>1.46956</td>
</tr>
<tr>
<td>Inotropic medication (Yes)</td>
<td>1.40856</td>
</tr>
<tr>
<td>Temperature (≤35.5°C or &gt;39°C)</td>
<td>0.91645</td>
</tr>
<tr>
<td>Heart rate (&gt;90 bpm)</td>
<td>0.67818</td>
</tr>
<tr>
<td>Haemoglobin (≤5.0 mmol/L)</td>
<td>1.09552</td>
</tr>
</tbody>
</table>

| Intercept (original)                      | -4.412803|
| Intercept (updated)                       | -3.135282|

The predicted probability of ongoing sepsis was calculated using the following formula:

\[ P = \frac{1}{1 + \exp(-3.135282 + 0.76695 \text{ (if diffuse contamination was present during initial surgery)} + 1.46956 \text{ (if no defecation)} + 1.40856 \text{ (if inotropic medication is needed)} + 0.91645 \text{ (if temperature ≤35.5°C or >39°C)} + 0.67818 \text{ (if heart rate >90 bpm)} + 1.09552 \text{ (if haemoglobin ≤5.0 mmol/L)}} \]