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ORIGINAL ARTICLE

A probabilistic model for the prediction of intra-abdominal infection after colorectal surgery

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Abstract

Aim Predicting intra-abdominal infections (IAI) after colorectal surgery by means of clinical signs is challenging. A naïve logistic regression modeling approach has some limitations, for which reason we study two potential alternatives: the use of Bayesian networks, and that of logistic regression model.

Methods Data from patients that had undergone colorectal procedures between 2010 and 2017 were used. The dataset was split into two subsets: (i) that for training the models and (ii) that for testing them. The predictive ability of the models proposed was tested (i) by comparing the ROC curves from days 1 and 3 with all the subjects in the test set and (ii) by studying the evolution of the abovementioned predictive ability from day 1 to day 5.

Results In day 3, the predictive ability of the logistic regression model achieved an AUC of 0.812, 95% CI = (0.746, 0.877), whereas that of the Bayesian network was 0.768, 95% CI = (0.695, 0.840), with a *p*-value for their comparison of 0.097. The ability of the Bayesian network model to predict IAI does present significant difference in predictive ability from days 3 to 5: AUC(Day 3) = 0.761, 95% CI = (0.680, 0.841) and AUC(Day 5) = 0.837, 95% CI = (0.769, 0.904), with a *p*-value for their comparison of 0.006.

Conclusions Whereas at postoperative day 3, a logistic regression model with imputed data should be used to predict IAI; at day 5, when the predictive ability is almost identical, the Bayesian network model should be used.

Keywords Probabilistic model · Intra-abdominal infection · Colorectal surgery

What does this paper add to the literature?

We performed a single center study to develop a statistical model that allows for estimating the probability of intra-abdominal infection after colorectal surgery with anastomosis considering the surgical approach, based on the evolution of postoperative analytical parameters. The statistical model described in this study makes it possible to predict IAI after a colorectal procedure with anastomosis with or without a derivative stoma, even in the presence of missing data, using either a Bayesian network or a logistic regression model with multiple imputation.

Introduction

Infectious complications after surgical procedures remain a major clinical problem in abdominal surgery. Most of the patients where an infection was initially neglected may end up developing sepsis or septic shock, both of which are associated with high rates of morbidity and mortality. An early diagnosis of severe infections and sepsis are thus vital.

Intra-abdominal infection (IAI) after colorectal surgery results in significant morbidity and mortality and has been shown to adversely affect long-term oncological outcomes after resection for cancer [1, 2]. Despite the recent advances in perioperative care, IAI still constitutes a significant proportion of morbidity after elective colorectal resections with prevalence rates ranging from 5 to 15% [3].

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It has been suggested in the literature that the systemic inflammatory response syndrome (SIRS) in the postoperative period simply reflects the pro-inflammatory state related with the surgical trauma. This is proportional to the degree of surgical stress the patient has undergone [4, 5] covering an early diagnosis of complications.

Enhanced Recover After Surgery (ERAS) management programs integrate multimodal perioperative interventions, which include the introduction of short-acting anesthetic agents, optimal pain and antiemetic control, and aggressive postoperative rehabilitation, as well as early oral nutrition and wandering. ERAS programs are usually implemented together with the use of minimal invasive surgical techniques such as laparoscopic or robotic approaches. These programs are designed to reduce physiological stress and facilitate an early return of the bodily function. They are also associated with early discharge, which in some cases may, in turn, be associated with an increased risk of post-hospital discharge diagnosis of postoperative infections and their treatment or with at least a higher rate of readmissions [3, 6]. There is a need for excluding complications after abdominal surgery so as to benefit early and safe discharge of our patients [7].

After a colorectal resection with anastomosis, the first clinical signs of sepsis are often non-specific or inaccurate. The more typical signs, such as hypotension or raise of the lactate levels, are usually found late or associated to multiorgan failure, which then increases the mortality rate [8, 9].

One of our objectives during colorectal surgery postoperative course is to achieve an early diagnosis of complications, since the subsequent early treatment can decrease the associated morbidity and mortality [10].

Identifying postoperative complications in surgery by means of abnormal clinical signs is extremely difficult and limited in the first days after surgery, since the effects of the surgical trauma, analgesia, etc., are confusing. These symptoms usually do not become apparent until there is a well-established infection. The same happens with the analytical parameters routinely used (haematological and basic biochemical analyses), which show no evidence of complication until there is an established infection or even organ failure [11].

According to clinical data, Bellows et al. found that neurological and pulmonary events are the earliest clinical sign of postoperative anastomotic leakage, but these tend to appear beyond the fourth postoperative day [12]. Fever, local peritonitis, and ileus have also been evaluated in this and other studies, but these either take even longer to appear (postoperative day 6) or are unreliable [13].

It is difficult to anticipate when such complications will occur, though an early diagnosis is essential to improve the prognosis.

Different studies have shown that C-reactive protein (CRP) and procalcitonin (PCT) can be used in the early diagnosis of sepsis, allowing for early action on the septic focus [14, 15]. A recent work by Stephensen et al. presents a logistic regression approach to the problem of predicting leakages from CRP measurements [16]. They develop as many logistic regression models as the number of days at which the CRP is measured, which, even with their promising results, is not easily scalable to the often-intricate missing data patterns in daily medical practice. On the other hand, the trajectory analysis is not accurate to diagnose anastomotic leakage although it demonstrates a good value for discharge in case of not increasing for more than 24 h in post-operative days 3 to 5.

For this reason, we propose two alternatives to the problem of missing data in our prediction task: the use of Bayesian networks, which natively handle missing data, and that of logistic regression models with multiple imputation.

Methods

This study was performed in accordance with the ethical standards of the institutional and regional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The prospectively collected database of the colorectal surgery unit was used. Between 2010 and 2017, we identified 799 patients who, treated for colorectal diseases, had undergone entero-enteric, entero-colic, colo-colic, or colorectal anastomoses (with or without protective loop ileostomies) or end colostomies. Six hundred and forty-four (644) of these patients met the inclusion criteria for participation in this study: (i) they had undergone entero-colic anastomosis or colorectal anastomosis (with or without protective ileostomy) and (ii) we had measured their CRP and PCT levels at, at least, postoperative days 1 and 3. Patients with entero-enteric anastomosis or with end colostomies were excluded from the analysis.

Data collection included (though was not limited to) the variables that are present in Table 1. The CRP and PCT levels at day 5 were not available for all the patients, as (i) their length of stay was shorter than 5 days, (ii) we had not measured those pieces of information or (iii) they had postoperative infectious complications before day 5. This indicates a "missing at random" mechanism: those without IAI do not have data from day 5 in a higher proportion than those with IAIs; hence, provided our statistical models include the IAI variable (in fact, it is the variable that we want to predict), there is no need for modeling the missing data mechanism. In the next subsections, we will see two models to alleviate the presence of missing data.

Table 1 Patient characteristics by IAI status

		With IAI ($N = 194$)	Without IAI ($N = 450$)	P[a]
Age (years)*	—	69.12 (10.87)	68.60 (11.42)	0.594
Sex	Female	61 (31.44)	181 (40.22)	0.035[b]
	Male	133 (68.56)	269 (59.78)	
Surgical procedure	Enterocolic anastomosis	79 (40.72)	155 (34.44)	0.057[b]
	Colorectal anastomosis	52 (26.80)	164 (36.44)	
	Colorectal anastomosis with Protective Ileostomy	63 (32.47)	131 (29.11)	
Surgical approach	Open	64 (32.99)	76 (16.89)	2.7×10^{-5}[b]
	Laparoscopic	53 (27.32)	141 (31.33)	
	Robotic	77 (39.69)	233 (51.78)	
CRP level (mg/dl)*	Day 1	11.75 (5.45)	8.66 (4.16)	1.9×10^{-14}
	Day 3	17.33 (8.39)	9.71 (5.78)	8.5×10^{-36}
	Day 5	14.62 (9.06)	5.01 (4.00)	4.1×10^{-51}
PCT level (ng/ml)*	Day 1	2.95 (10.32)	1.03 (2.78)	2.9×10^{-4}
	Day 3	4.65 (15.76)	1.44 (6.17)	2.2×10^{-4}
	Day 5	2.87 (7.88)	0.47 (1.82)	8.7×10^{-8}
Day of discharge	Day 4 or earlier	28 (14.43)	85 (18.89)	0.173[b]
	Day 5 or after	166 (85.57)	365 (81.11)	

Values in parentheses are percentages unless stated otherwise

CRP C-reactive protein, *PCT* procalcitonin, *IAI* intra-abdominal infections

*Values are mean (SD)

[a]Two-sided Student's t-test, except

[b]Pearson's χ^2 test

IAI was defined as the presence of either localized (abscess) or uncontained (diffuse) infection in the abdomen. IAI was positively registered in the database when there was either an image test (ultrasound or computerized tomography scan) or surgical technique confirming the diagnosis of IAI.

Imputation in regression models

Given the fact that we want to predict a binary variable as a function of predictors in the absence of complete data, we can impute missing data for those predictors. Imputation consists in searching for patterns between the complete and the incomplete variables. All our variables are complete except CRP and PCT at day 5, which are continuous variables, whose distribution conditioned on the rest of the variables can be modeled via a multivariate lognormal distribution.

Bayesian networks

A Bayesian network is a statistical model that represents a set of variables and their conditional dependencies as nodes and edges, respectively, in a directed acyclic graph. Each node X is associated with a function $\Pr(X|\mathrm{Pa}(X))$ that answers the question "Given a set of values for X's parent variables in the graph, what is the probability distribution of X?" Thus, a BN defines the joint probability distribution of the variables $X_1, \ldots, X_n$ as

$$\Pr\left(X_1, \ldots, X_n\right) = \prod_{i=1}^{n} \Pr\left(X_i \middle| Pa(X_i)\right) \quad (1)$$

Consider the 3-node BNs (i) $X \to Y \to Z$, (ii) $X \leftarrow Y \to Z$, and (iii) $X \to Y \leftarrow Z$, whose joint probability distributions are, by Eq. 1,

i. $\Pr(X, Y, Z) = \Pr(X)\Pr(Y|X)\Pr(Z|Y)$,
ii. $\Pr(X, Y, Z) = \Pr(X|Y)\Pr(Y)\Pr(Z|Y)$ and
iii. $\Pr(X, Y, Z) = \Pr(X)\Pr(Y|X, Z)\Pr(Z)$.

The first two BNs imply that X and Z are *conditionally independent* given Y—once we observe the value of Y, that of X becomes irrelevant to the probability distribution of Z and vice versa—whereas the third BN, that X and Z are *conditionally dependent* given Y.

Statistical analysis

We split the dataset into two subsets: (i) that for training the models and (ii) that for testing them. To do so, we sorted the patients in chronological order of surgery and selected, approximately, the first 70% for the training set and the remaining 30% for the test set.

We built the models with the information regarding the biomarkers from days 1 to 5 and the surgery characteristics. We thus ended up with three regression models: one with only considers the information at day 1; another one, at days 1 and 3; and a third one, at days 1, 3, and 5. We imputed the missing data by means of a multivariate log-normal distribution.

As for the Bayesian network, we built it from the expert knowledge that we collected from the scientific literature and our daily clinical practice (see Fig. 1).

Once we built and trained the models, we evaluated them in the test set and compared their predictive abilities by means of ROC curves and their differences in area under the ROC curve (AUC).

Imputation and statistical analysis were performed in Stata 16, whereas the building, training, and testing of the Bayesian network model were performed with Bayes Server 9.

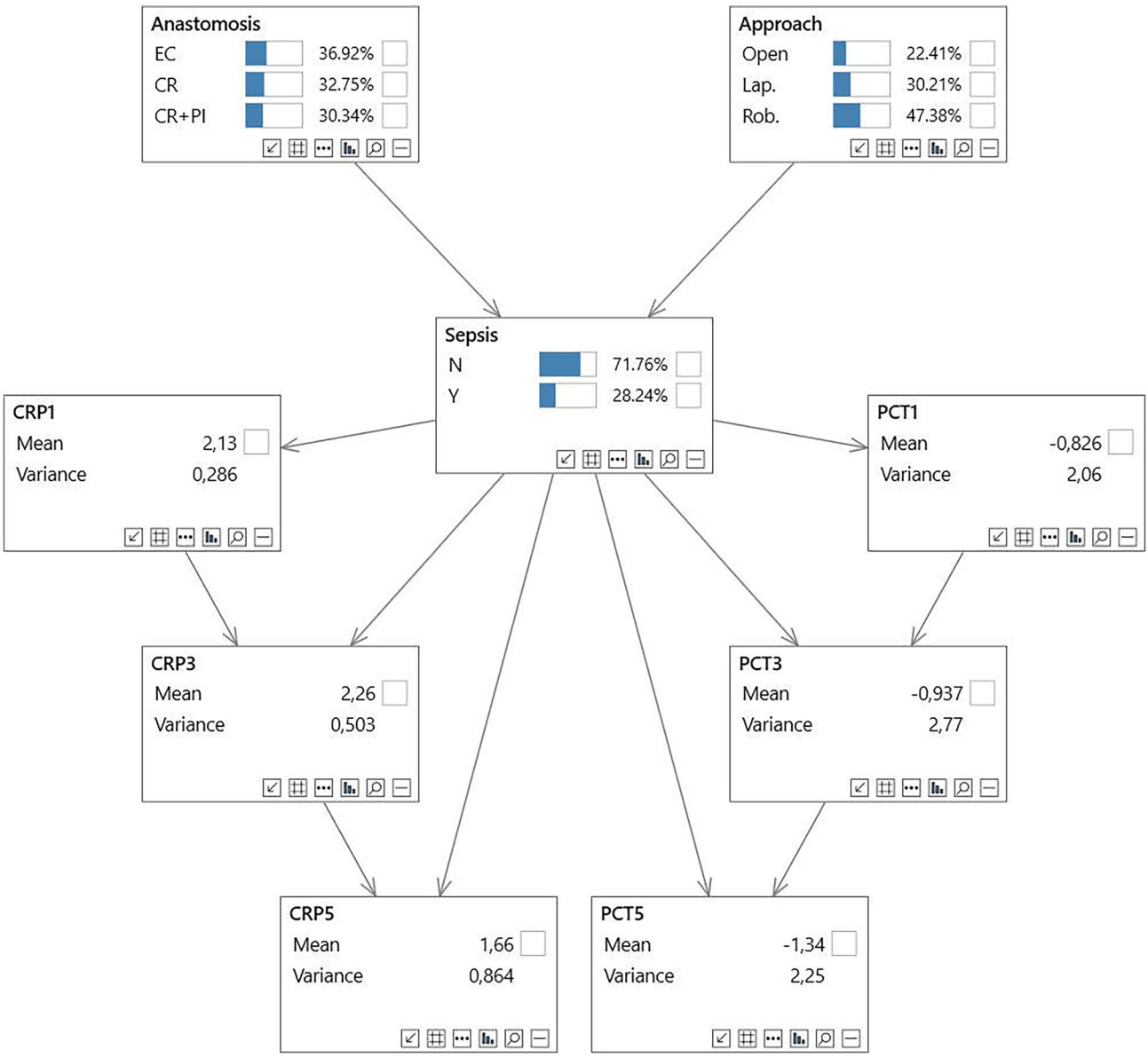

Fig. 1 Bayesian network model

Biomarker measurements

PCT was measured by electrochemiluminescence (Test Elecsys BRAHMS PCT eCobas 411 equipment (Roche)). The measurement range was from 0.02 to 100 ng/ml.

CRP was measured using immunoturbidimetry technology in Dimension Rxl equipment (Siemens) with a sensitivity of 0.05 mg/dl.

Results

We tested the predictive ability of the models proposed in two different ways: (i) by comparing the ROC curves from days 1 to 3 with all the subjects in the test set and (ii) by studying the evolution of such a predictive ability from days 1 to 5 as more information was measured. In this sense, we applied the second comparison to those patients of the test set whose length of stay was, at least, 5 days.

Figures 2 and 3 account for the first experimentation scenario. In the case of day 1, the area under the ROC (AUC) of the logistic regression model was—please note that we provide its estimate along with its 95% confidence interval in parentheses—0.635 (0.545, 0.725), where that of the Bayesian network was 0.681 (0.595, 0.767). We did not find evidence that supported a difference in predictive ability for both models at day 1 ($p = 0.097$).

In the case of day 3, the predictive ability of the logistic regression model increases dramatically, with an AUC of 0.812 (0.746, 0.877), whereas that of the Bayesian network also increases, but not so remarkably. Its AUC is 0.768 (0.695, 0.840). Nevertheless, we did not find evidence that supported a difference in predictive ability for both models at day 3 ($p = 0.097$).

Regarding the second experimentation scenario, Figs. 4 and 5 gather the evolution in predictive ability of the two models in those patients who had a length of stay of, at least, 5 days and, therefore, we were able to measure their

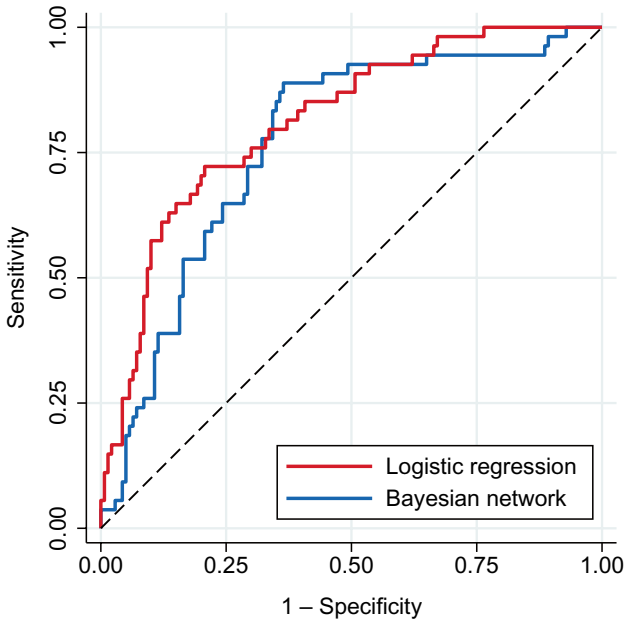

Fig. 3 ROC curve comparison at day 3

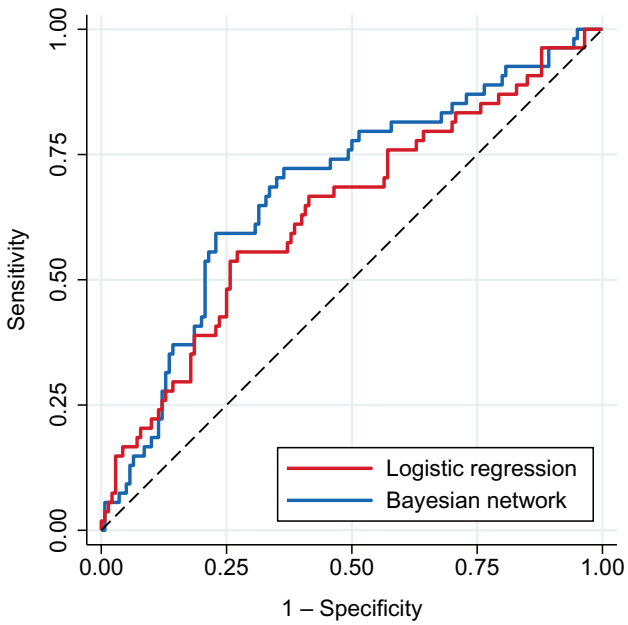

Fig. 2 ROC curve comparison at day 1

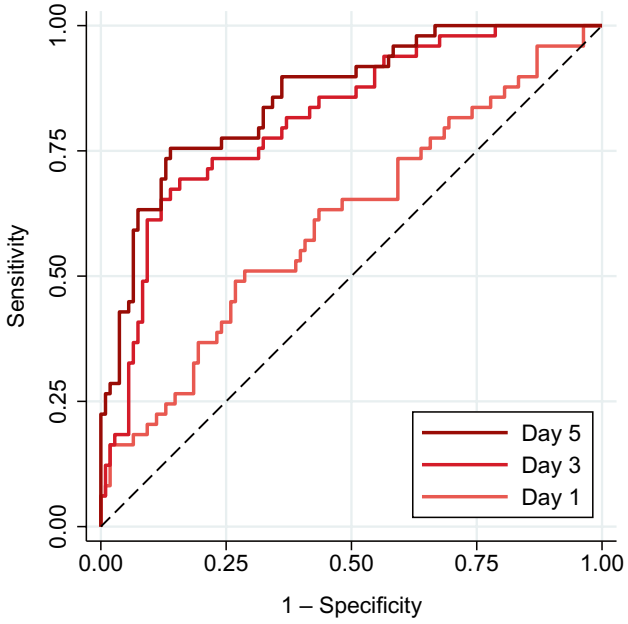

Fig. 4 Evolution in the predictive ability of the logistic regression model

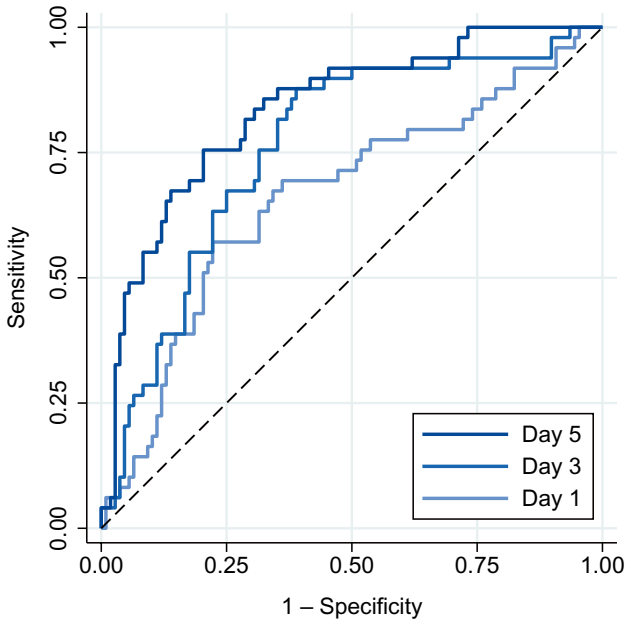

Fig. 5 Evolution in the predictive ability of the Bayesian network model

CRP and PCR levels at days 1, 3, and 5. We observe, also in this subsample, the steep increase in the predictive ability of the logistic regression model from days 1 to 3. Such was the case that we did not find evidence that supported a difference in predictive ability for this model from day 3 to 5: AUC(Day 3) = 0.814 (0.743, 0.886), AUC(Day 5) = 0.858 (0.796, 0.920), with $p = 0.105$.

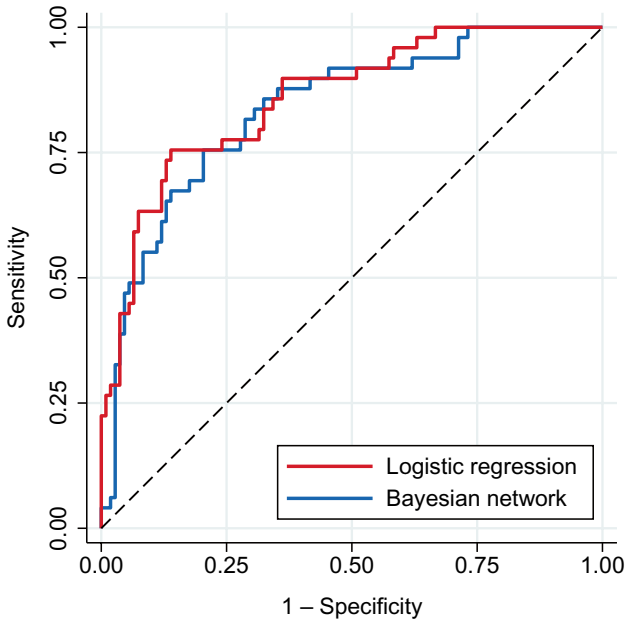

Fig. 6 ROC curve comparison at day 5

On the other hand, Fig. 5 accounts for the evolution in predictive ability of the Bayesian network model. In this case, it increases as information is available as days pass, and does present a significant difference in predictive ability from days 3 to 5: AUC(Day 3) = 0.761 (0.680, 0.841) and AUC(Day 5) = 0.837 (0.769, 0.904), with $p = 0.006$.

Finally, Fig. 6 highlights the fact that we did not find enough evidence to support a significant difference in predictive ability between the logistic regression model and the Bayesian network model at day 5 ($p = 0.325$).

Discussion

It has been deeply sought that an early diagnosis of postoperative complications allows for an early goal-directed treatment. In hospital practice, different clinical signs of infection, such as temperature, heart rate, respiratory rate, and analytical data (platelet count or white blood cell), have been used.

CRP has been used for years as a biomarker of septic complication [17], but its specificity is questionable, since its rise also expresses inflammatory response. PCT has been proposed as a more specific marker of sepsis, with a better predictive ability compared with CRP [18], but equally questionable [19].

Several studies in colorectal surgery corroborate the connection between an increase in CRP and the development of postoperative infectious complications such as anastomotic leak or intra-abdominal abscesses [20–24].

The use of CRP as an accurate predictive tool to ensure an early and safe discharge has been well-established. However, one of the potential flaws of CRP as a diagnostic marker is that although a nonspecific inflammatory marker, the rise in its levels may simply be due to inflammation rather than the underlying sepsis. This has led to an increased interest in PCT as it is a more specific predictor of sepsis: unlike CRP, the release of PCT is induced by bacterial endotoxins specifically.

Different meta-analyses [15, 25] have shown a low positive predictive value and a high negative predictive value for CRP. PCT is widely used in emergency services and critical care units both for the diagnosis of septic patients and to assess their prognosis. Recently, several studies [26, 27] have described PCT as a good predictor of IAI after colorectal surgery. The highest diagnostic accuracy for both CRP and PCT has been shown to occur in the 5th postoperative day.

Most of the literature refers to cut-off points for CRP and PCT, but recent evidence has revealed a potential association between colorectal anastomotic leak, as defined by the need for intervention, and the trajectory of PCT and CRP [28].

This kind of analysis may help correct the bias that other factors of the procedure can cause, such as, apart from the complications, the type of surgical approach carried out [29].

We built two types of models that aimed to predict IAI complications after colorectal surgery considering the surgical approach, while addressing the problem of missing data (CRP/PCT) after colorectal surgery. Both models present advantages and disadvantages: on the one hand, it is well-known that logistic regression is to be chosen over its Bayesian network counterpart when one has complete data, but the former suffers from the inability of treating missing data flexibly. To alleviate such an inability, we imputed those missing data when appropriate, thus creating three logistic regression models: that of day 1, that of day 3, and that of day 5.

On the other hand, Bayesian networks, due to their own nature, are capable of handling missing data natively, but it is quite common for them to show lower performance in comparison with logistic regression models in the presence of complete data. However, Bayesian networks allow for introducing dependency relationships among variables in a simpler way, both learning them from data or given previous expert knowledge.

Considering our results, we can state that both models are compatible in terms of predictive ability when compared at each day; that is, there are no significant differences between them at day 1, or at day 3, or at day 5. Nonetheless, it is remarkable that from days 1 to 3, the logistic regression model experiences a considerable gain in predictive ability that, despite not having significant differences with the Bayesian network at that day, does not provide either a significant difference with respect to the predictive ability of the very logistic regression model at day 5.

The purpose of the probabilistic model can be twofold: (i) aiming at confirming the diagnosis of IAI—which may involve asking for further tests, such as ultrasound or CT scans—and (ii) ensuring an early safe discharge. The inclusion of these probabilistic models in electronic medical records for predictive score calculation during clinical decision making might increase patient safe postoperative management. Using the algorithm presented in this manuscript could be helpful for this objective.

Should our goal be to reduce the number of days that a patient stays at the hospital, the logistic regression model seems to raise itself as a good candidate in the presence of complete data. However, we are aware of the fact that clinical practice is far from ideal: it is quite common to be in a situation in which an analysis was performed to a patient at day 3, but was not at day 1. In such a case, a logistic regression model able to contemplate the absence of data at day 1 must be built from scratch, trained again and, in case we had to deal with more missing data, we should impute them again. This is, most of the time, unfeasible for daily clinical practice, for which reason we cannot rule out the use of Bayesian networks, which are capable of computing—with the obvious loss in predictive ability—the probability of IAI despite not having complete data and without the need for rebuilding the model.

Even though the application of PCT can be expensive, early diagnosis of major complications and an early discharge of those patients in whom it is normal could make its use efficient. As the Bayesian network model would work even without the PCT, its use would not be imperative anyway.

Thus, we recommend a sort of a hybrid model: should one have complete data, the logistic regression model with imputed data must be used, above all at day 3; otherwise, or if at day 5, when the predictive ability is almost identical, the Bayesian network model should be used.

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