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World J Gastrointest Surg 2024 October 27; 16(10): 3074-3380



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The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS, World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGS* as 1.8; JIF without journal self cites: 1.7; 5-year JIF: 1.9; JIF Rank: 123/290 in surgery; JIF Quartile: Q2; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Zi-Hang Xu*, Production Department Director: *Xiang Li*, Cover Editor: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Peter Schemmer

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

October 27, 2024

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Can serious postoperative complications in patients with Crohn's disease be predicted using machine learning?

Andrew Paul Zbar

Specialty type: Surgery

Provenance and peer review:
Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Liu Q

Received: March 19, 2024

Revised: July 16, 2024

Accepted: September 5, 2024

Published online: October 27, 2024

Processing time: 192 Days and 17.6 Hours



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Abstract

The routine introduction of novel anti-inflammatory therapies into the management algorithms of patients with Crohn's disease over the last 2 decades has not substantially changed the likelihood of ultimate surgery. Rather it has delayed the operative need and altered the presentation phenotype. The prospect of complications continues to remain high in this modern era but depending upon the cohort assessed, it remains difficult to make strict comparisons between individual specialist centres. Those patients who present rather late after their diagnosis with a septic complication like an intra-abdominal abscess and a penetrating/fistulizing pattern of disease are more likely to have a complicated course particularly if they have clinical features such as difficult percutaneous access to the collection or multilocularity both of which can make preoperative drainage unsuccessful. Equally, those cases with extensive adhesions where an initial laparoscopic approach needs open conversion and where there is an extended operative time, unsurprisingly will suffer more significant complications that impact their length of hospital stay. The need for a protective stoma also introduces its own derivative costs, utilizing a range of health resources as well as resulting in important alterations in quality of life outcomes. Having established the parameters of the problem can the statistical analysis of the available data identify high-risk cases, promote the notion of centralization of specialist services or improve the allocation of disease-specific health expenditure?

Key Words: Crohn's disease; Postoperative complications; Clavien-Dindo; Machine learning; Outcome

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Core Tip: Significant postoperative complications continue to be a challenge in those who come to operation for Crohn's disease. Modern management with immunosuppressive treatment has only significantly delayed surgery rather than prevented the need for operation. Machine learning provides new algorithms that supersede logistic regression of prognostic outcome factors in retrospective analyses. Multi-institutional prospective studies are required to better identify those patients where major complications are likely and where there will be a requirement for postoperative critical care and higher health care expenditure.

Citation: Zbar AP. Can serious postoperative complications in patients with Crohn's disease be predicted using machine learning? *World J Gastrointest Surg* 2024; 16(10): 3358-3362

URL: <https://www.wjgnet.com/1948-9366/full/v16/i10/3358.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v16.i10.3358>

TO THE EDITOR

In Crohn's disease over recent years there have been important advances for patients in diagnosis along with the more routine use of novel immune therapies and the specialization and development of regional centres of excellence. Despite these improvements, there still remain significant challenges for those patients who are destined to undergo surgical treatment[1]. This issue is, however, complex. Although the playing field may have changed with the introduction of anti-tumor necrosis factor, anti-interleukin and anti-integrin biologic therapies, there is a general acceptance that medical treatments overall have not effectively altered the ultimate rate of surgical intervention[2-5]. Given the nature and patterns of disease presentation, medical management has, however, resulted in fewer patients coming to surgery with poor nutrition. Furthermore, there are more cases where there has been steroid sparing and better control of intra-abdominal sepsis, particularly in those presenting with a penetrating disease phenotype[6-8].

With modern management effectively only delaying surgery, those risk factors which directly influence postoperative complications become particularly important. Data concerning the impact both of steroids and of immunomodulatory therapies on the rate and type of postoperative complication is, however, somewhat conflicted. In this regard the results of the recent PUCCINI trial designed to examine the safety of preoperative tumor necrosis factor-inhibitor therapy in those with inflammatory bowel disease undergoing abdominal surgery (carried out across 17 Crohn's and Colitis Clinical Research Alliance institutions), has shown no increase in the overall postoperative infection risk[9]. These data are in contradistinction to several earlier meta-analyses that had suggested the opposite result[10-12]. Part of this disparity is dependent upon the heterogeneity of the studies reported as well as comparatively small numbers of surgical candidates who then received a variety of biologic agents. Concerning this latter point, there is for example evidence to suggest that anti-integrin therapy (vedrolizumab targeting alpha-4 beta-7) can substantially increase the complication risk[13]. By contrast, even though corticosteroid use has been implicated in the rate of postoperative septic complications following intestinal resection[14,15], high quality evidence is still lacking. The interpretation of these types of reports requires considerable caution since outcomes are influenced by any attempt within individual studies to reduce the steroid dosage (or indeed to suspend their use) prior to surgery. It is evident that many studies fail to record either the steroid dose used or the timing of dosage minimization.

Prognostic factors for postoperative complications

In a timely study by Wang *et al*[16] reported in this current journal edition, the authors have provided retrospective data of both a training and a validation cohort of unselected Crohn's disease patients managed surgically over a 5-year period in a specialized tertiary referral centre. The small complication rate (13/259; 5.01%) does make interpretation and extrapolation difficult but would suggest that a low albumin and a high Crohn's disease activity index are correlators for important postoperative complications. Unsurprisingly, these patients are linked in the database towards a higher rate of open conversion from a laparoscopic start, as well as by longer operative times and greater recorded intraoperative blood loss. Although Crohn's clinical severity indices are not universally used, (in part because of their subjective elements and debate concerning cut-off values), a worse clinical score has not unexpectedly been associated with worse outcomes. This is a particular finding for penetrating and perforating disease phenotypes[17]. The authors' finding that preoperative hypo-albuminaemia correlates with an increased propensity towards complications particularly in emergency cases reflects other single-institution reports where nutritional deficiency before surgery (frequently combined with limited control of intra-abdominal sepsis and recent steroid use), increases the postoperative complication risk[18]. This type of finding has been confirmed in a recent meta-analysis[19]. As suggested by the authors, optimization of malnourished cases with enteral nutrition can influence the immune suppressant-free interval and the need in some cases for urgent surgery. This beneficial impact will then secondarily affect the recorded rate of complications as well as the use of protective stomas, the length of hospital stay (LOHS) and potentially the need for later repeat surgery[20].

There are of course, innumerable studies demonstrating the benefits for patients of a laparoscopic approach towards Crohn's resection with all of the accompanying advantages of minimally invasive surgery encompassing a shorter LOHS, a more rapid initiation after surgery of oral feeding and a faster return to work[21,22]. The data also show that emergency surgery is more frequently accompanied by complications although the authors quite rightly recognize that the numbers are too small to draw meaningful conclusions. Population-based studies do, however, show that although rarely re-

quired, emergency cases risk significant complications[23]. Concerning a related point, data that includes those patients where surgery takes place closer to the original diagnosis will tend to skew such reports away from the complicated case and towards less use of biologics[24,25]. Although the cumulative probability of steroid use is reduced in those patients operated upon earlier[26], this issue may be complicated by a reduced overall efficacy of certain biologic therapies such as certolizumab when there is an extended disease duration[27].

The findings reported by the authors that emergency surgery, a low albumin, a longer operating time and the need for laparoscopic-to-open conversion all correlate with a longer LOHS is well made, reflecting the overall complexity of any individual case. These data are confirmed in a recent study reported by Luong *et al*[28], in which as expected there is an association between the incidence and type of postoperative complications and the LOHS. It remains to be seen whether those factors identified with a complicated course (older age, the presence of a preoperative intra-abdominal abscess, prior abdominal surgery, the intraoperative detection of pockets of infection and laparoscopic conversion), can consistently act as surrogates in large, prospective multi-institutional studies for an expected worse clinical outcome after surgery[29,30].

The need for repeat surgery in up to one-third of cases over a decade of follow-up reflects the incidence of medically refractory cases as well as those complicated abscesses and fistulae, repeat strictures and cases of toxic megacolon[31]. Analysis is of course dependent upon the patients assessed where inclusion of these groups will substantially increase the likelihood of an open conversion and will lead to an increase in the recorded operating times. This may explain why some of the available data concerning the relationship between complications and open conversion alone are conflicting[32,33]. As the authors have pointed out in patients with extensive intra-abdominal adhesions, long operations result in significant changes in the prevailing microbiota, an increase in the risk of intestinal ischaemia and contribute to surgeon fatigue[34]. Moreover, in some cases the control of intra-abdominal sepsis by percutaneous drainage in the immediate preoperative period is inadequate, relying upon technically safe accessibility for a well-defined, unilocular abscess collection[35].

Machine learning in the postoperative Crohn's patient

The authors have shown that specific machine learning of risk factors using random forest modelling improved their sensitivity, specificity and the operating performance characteristics obtained over conventional logistic regression for the diagnosis of significant Clavien-Dindo complications after surgery. In so doing, they have leveraged the SHAP analysis to provide a visual recognition of clinical (and more importantly) modifiable predictors for a complicated course. In such an analysis we should, however, take care. It is accurate to suggest that the use of complex modelling imputation will capture more reliable predictive patterns than logistic regression analyses[36,37]. In these patients the data input space is complex first requiring us to determine our goals using such modelling by clearly defining the timing of data inclusion. We need up front to decide how we intend to collect our data and which data precisely to use for decision making purposes. The incorporation of preoperative as well as intraoperative data creates a different approach towards outcome with preoperative information (laboratory results, patient demographics, clinical features) used as a complication predictor. Perioperative combined data on the other hand is potentially able to address a specific care management programme or to influence a smoother patient handover from the operating room to a critical care environment.

Further, how we handle missing data will affect the impact that 'missingness' has on the performance of an individual model. Put another way, how rapidly do certain models reach their asymptotes when missing information is included? This type of analysis naturally leads us to inquire about the comparative performance of other statistical techniques such as the gradient boosting tree which is potentially capable of outperforming a random forest approach by correcting errors in weak decision trees that are more readily split into simpler binary options (called decision stumps). Put simply, for the data imputed we should always ask not only what is our clinical aim but how within that defined scope can we best minimize bias? It should also be remembered that certain complications may be relatively rare so that when data are randomly split into training and validation groups there will always be a limit to how these findings can be translated into other health care environments. Many studies will report small numbers in particular subgroups limiting the clinical utility of predictors in patients who then undergo a particular operation and who afterwards experience a very particular complication. In Crohn's disease, the interpretation of all of these data is fraught with confounding and overlapping variables and information obtained retrospectively from a single centre will always make strict comparisons and the transferability of the conclusions rather difficult. It is accepted, however, that amongst these data the small sampling provided by a single institution represents an important limitation in interpretation of such a study.

CONCLUSION

Issues surrounding surgical indications, the impact of delays in surgery resultant from the use of biologics, the influence of discrete biologic therapies when used in combination or alone and the construction of a diverting stoma each affect the patient trajectory. We might more readily accept that predicting complications impacting hospital stay and patient quality of life more likely reflects disease severity and presentation pattern rather than any particular medical management alternatives. Despite these limitations, an expansion of this kind of data obtained from multiple surgical environments and the prospective weighted validation of individual prognostic factors through the establishment of regional registers could certainly have significant economic benefits. Advantages for this approach will pragmatically be seen in the allocation of health resources and in informing regional Health Administrative Service providers of the merits in centralizing specialist services.

FOOTNOTES

Author contributions: Zbar AP wrote and conceived of this submission.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

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S-Editor: Wang JJ

L-Editor: A

P-Editor: Xu ZH

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