84049_Auto_EditedC.docx

Case Control Study

Machine learning model for prediction of low anterior resection syndrome following laparoscopic anterior resection of rectal cancer: A multicenter study

Wang Z *et al*. Prediction model for major LARS

Zhang Wang, Sheng-Li Shao, Lu Liu, Qi-Yi Lu, Lei Mu, Ji-Chao Qin

Abstract

BACKGROUND

Low anterior resection syndrome (LARS) severely impairs patient postoperative quality of life, especially major LARS. However, there are few tools that can accurately predict major LARS in clinical practice.

AIM

To develop a machine learning model using preoperative and intraoperative factors for predicting major LARS following laparoscopic surgery of rectal cancer in Chinese populations.

METHODS

Clinical data and follow-up information of patients who received laparoscopic anterior resection for rectal cancer from two medical centers (one discovery cohort and one external validation cohort) were included in this retrospective study. For the discovery cohort, the machine learning prediction algorithms were developed and internally validated, and in the external validation cohort, we evaluated the trained model using

various performance metrics. Further, the clinical utility of the model was tested by decision curve analysis.

RESULTS

Overall, 1651 patients were included in the present study. Anastomotic height, neoadjuvant therapy, diverting stoma, body mass index, clinical stage, specimen length, tumor size, and age were the risk factors associated with major LARS. They were used to construct the machine learning model to predict major LARS. The trained random forest (RF) model performed with an area under the curve of 0.852 and a sensitivity of 0.795 (95%CI: 0.681-0.877), a specificity of 0.758 (95%CI: 0.671-0.828) and Brier score of 0.166 in the external validation set. Compared to the previous pre-operative LARS score model, the current model exhibited superior predictive performance in predicting major LARS in our cohort (accuracy of 0.772 for the RF model *vs* 0.355 for the pre-operative LARS score model).

CONCLUSION

We have developed and validated a robust tool for predicting major LARS. This model could potentially be used in the clinic to identify patients with a high risk of developing major LARS and then improve the quality of life.

Key Words: Machine learning; Low anterior resection syndrome; Rectal cancer; Laparoscopy

Wang Z, Shao SL, Liu L, Lu QY, Mu L, Qin JC. Machine learning model for prediction of low anterior resection syndrome following laparoscopic anterior resection of rectal cancer: A multicenter study. *World J Gastroenterol* 2023; In press

Core Tip: We developed and externally validated a machine learning-based prediction model that integrated preoperative and intraoperative risk factors as input features and

showed satisfactory predictive performance in Chinese patients. According to the decision curve analysis, patients with major low anterior resection syndrome (LARS) would have a net benefit superior to "treat all" or "treat none" with a range of threshold probabilities by using the model. This study provides a new tool for predicting major LARS, which can be potentially used for rectal cancer patients to acquire early postoperative consultation and strengthen self-management to improve their quality of life.

INTRODUCTION

With advances in surgical techniques and the introduction of a multi-disciplinary approach, sphincter-saving procedure for rectal cancer has increased[1], with up to 50%-80% of rectal cancer patients undergoing this procedure[2], compared with only 25% before the circular stapling device was widely used[3]. However, low anterior resection syndrome (LARS), a postoperative complication that seriously impairs patients' quality of life, has also increased[4,5], and 70%-90% of these patients undergoing sphincter-saving procedures have developed LARS[2]. The majority of LARS may go into remission within a variable interval from 6 to 18 mo following surgery[6,7]; however, beyond this point further improvements may be impossible and the complication may become irreversible. It is reported that ~40% of patients with major LARS remain to be 'toilet dependent', which results in a low quality of life[8,9]. Early management of medical intervention for major LARS, such as conservative drugs, transanal or transtomal irrigation, pelvic floor rehabilitation, biofeedback and sacral nerve stimulation, can improve LARS symptoms[10-14]. Therefore, it is important to identify the patients who are at a high risk of developing major LARS after surgery. A recent research has established a model based on preoperative risk factors to predict a LARS score for improving patient preoperative education and counseling[15]; however, it failed to achieve an accurate prediction when it was applied to other populations[16]. Furthermore, certain intraoperative factors which were previously reported as important contributors to LARS, were not included in this aforementioned model[17,18].

Due to better vision and less surgical trauma[19], laparoscopic surgery has improved the postoperative course in the treatment of rectal cancer and was widely applied in China. In theory, laparoscopic surgery ensures minimal surgical trauma and improve postoperative patient recovery as well as functional bowel outcome. However, there is still no tool to predict LARS in Asian patients who receive laparoscopic surgery. Artificial intelligence (AI) is an innovative modeling technology and has produced promising results; our previous studies have shown that AI algorithms allow for good discrimination of anastomotic leakage and would be helpful in assisting surgeons'

decision-making[20,21]. Therefore, the present study aimed to develop a machine learning model based on AI technology using preoperative and intraoperative factors for predicting major LARS following laparoscopic surgery of rectal cancer in Chinese populations. This model was created to guide early postoperative management of medical intervention, and improve patient postoperative consultation and quality of life.

MATERIALS AND METHODS

Data and participants

The present study included a discovery cohort and an external validation cohort. To develop the machine learning model, clinical data of 2120 patients with rectal cancer who received laparoscopic anterior resection in the Department of Gastrointestinal Surgery, Tongji Hospital, Huazhong University of Science and Technology from January 1st 2012 to December 31st 2020, were reviewed and collected. For external validation, data from 289 patients from the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture affiliated to Wuhan University between January 1st 2012 and December 31st 2020, were collected, with the same criteria. The present study was performed according to the guidelines of the Declaration of Helsinki and approved by the ethics committees of Tongji Hospital, Huazhong University of Science and Technology and The Central Hospital of Enshi Tujia and Miao Autonomous Prefecture. The requirement for informed consent was waived due to the retrospective nature of the study.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age ≥ 18; (2) primary rectal adenocarcinoma located 0-15 cm from the anal verge; (3) patients without communication difficulties. The exclusion criteria were as follows: (1) patients who had their diverting stoma open; (2) less than one year after laparoscopic anterior resection or after stoma reversal; (3) patients with a history of abnormal bowel function, including drug-induced diarrhea, a chronic history of constipation, irritable bowel syndrome and history of pelvic injury; (4) patients

with local recurrence within one year after surgery; and (5) missing data, death or lost to follow-up.

Candidate variables

In order to develop the early postoperative major LARS prediction model, only the clinical preoperative and intraoperative variables of each patient were included. The variables were as followings: age at surgery, gender, body mass index (BMI), hypertension, diabetes, previous abdominal surgery, neoadjuvant therapy, American Society of Anesthesiologists (ASA) classification, tumor size (cm), clinical stages, anastomotic height (cm), diverting stoma, specimen length (cm). Two authors independently completed the collection and collation of clinical data, and conflicting data were documented and confirmed by a final discussion. Anastomotic height was defined as the distance between anastomosis and anal verge measured using digital rectal examination, computed tomography or magnetic resonance imaging. Specimen length was defined as the length of the bowel removed during surgery.

Outcome

The Chinese version of the LARS score system was used to evaluate postoperative intestinal function[22], which is described by five questions concerning intestinal function. Each response was weighted and given a score according to the severity of the patient's symptoms. Scores of 0-20 indicated no LARS, 21-29 indicated minor LARS, and 30-42 indicated major LARS. All the participants were followed up by telephone, short message service and outpatient or inpatient visits using a LARS score questionnaire from November 1, 2021 to May 1, 2022. LARS scores of each participant at one year after anterior resection or after stoma reversal were obtained. To highlight major LARS, patients were classified into two groups according to LARS score, one with major LARS and another with no or minor LARS.

Feature selection

Excessive variables could lead to adverse predictions and be inconvenient in an application. The Boruta algorithm can address the minimal optimization problem of multidimensional clinical features in feature selection[23]. Thus, feature selection was conducted using the Boruta algorithm. The algorithm can screen out all the variables associated with the ground truth. The importance of the features was quantified by repeated iterations based on shadow feature creation, and some weakly correlated features were removed. Finally, the selected features, combined with clinical experience, were used as predictors. R software and Boruta packages (7.0.0) were used for feature selection (R version 4.1.2[2021-11-01]).

Sample size

The one-in-ten rule is a generally accepted rule for estimating the minimum sample size[24]. According to at least ten events per variable, at least 325 to 667 patients were required in the discovery cohort for the 13 predictor variables, with an estimated event (major LARS) rate of 30%-50% and a lost follow-up rate of 20%-35%.

Machine learning algorithms

In the present study, four prevailing machine learning algorithms, including logistic regression (LR), random forest (RF), support vector machine (SVM) and extreme gradient boosting (XGBoost), were employed to develop the predictive models. Machine learning algorithms based on AI can overcome the limitations of traditional linear models by combining clinical nonlinear features. The participants from Tongji Hospital were randomly divided into a training set and a testing set at a ratio of 8: 2. To gain high-performance models, hyperparameter adjustment was adopted using a grid search approach. To balance sensitivity and specificity, the optimal Youden index (cut-off value) was calculated *via* maximizing the value of sensitivity + specificity - 1[25]. The area under the curve (AUC) and Brier scores, which represent the discrimination and calibration power of the prediction model, were calculated. The Brier score measures the difference between the predicted probability and the ground truth[26], and a value of the Brier Score

closer to 0 indicates a better calibration. In addition, to assess the clinical utility of the prediction model, decision curve analysis was used, which can determine whether patients benefit from using predictive models in clinical practice[27]. All machine learning algorithms were implemented using Python (version 3.9.7) with the scikit-learn (version 0.24.2) package.

Statistical analyses

The continuous variables are presented as mean ± SD and categorical variables as the count (%). A one-way ANOVA with post hoc contrasts by the student-Newman-Keuls test was used to compare the differences between the continuous variables. For categorical variables, as appropriate, χ^2 or Fisher's exact test was used. All P values were reported as two-tailed, and $P < 0.05$ was considered as statistical significance. 95%CI for the AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy of the four models were calculated using IBM SPSS Statistics 20.0 (IBM Corp, Armonk, NY, United States) or Vassar Stats (online tool, http://vassarstats.net/index.html).

RESULTS

Summary of demographic and clinical characteristics for training, testing and external validation sets

Figure 1 presents the patient flow chart. A total of 1651 eligible cases were included, with 1163 subjects included in the training set, 291 subjects included in the testing set and another 197 subjects in the external validation set. Comparisons between the training, testing and external validation sets are presented in Table 1. The mean age of the 1163 patients in the training set was 57.6 years and 59.7% were men. For the testing and the external validation sets, the mean age was 57.6 and 59.7 years, and 56.0% and 53.8% were men, respectively. Major LARS was observed in 37.2% of patients in the training set, 35.1% in the testing set, and 37.1% in the external validation set.

Risk factors associated with major LARS

The importance of all the included variables calculated by the Boruta algorithm was shown in Figure 2A. Boruta calculates variables that are both strongly and weakly relevant to provide the best prediction accuracy. The blue boxes were shadow features automatically generated by the algorithm and were not included in the analysis. As the data indicated that anastomotic height, neoadjuvant therapy, diverting stoma, BMI, clinical stage, specimen length, tumor size and age were selected as significantly relevant to major LARS.

Model development in the training set

The LR, RF, SVM and XGBoost algorithms were trained using the eight strongly related variables, and the AUCs, sensitivities, specificities, PPVs, NPVs and accuracies were calculated (Figure 2B and C). The RF model exhibited optimal diagnostic performance (AUC = 0.869), and the optimal cut-off was 0.406. Therefore, the RF model was used for subsequent analysis. The details of the predictions generated by the RF model using the optimal threshold were shown in Figure 2D. Additionally, the predicted probabilities for major LARS were significantly relevant to the ground truth in the training set ($P < 0.001$) (Figure 2E).

Performance of the RF model in the testing set

We tested the performance of the RF model in the testing set. The results demonstrated that the RF model performed with a favorable discrimination ability (AUC = 0.870, 95%CI: 0.833-0.901) (Figure 3A). The details of the predicted outcomes were presented in Figure 3B. Subsequently, the comparison of the predicted probabilities between the major LARS and no/minor LARS groups was conducted, and significant differences were observed (Figure 3C). Furthermore, a decision curve was plotted to evaluate whether using the RF model in the clinic would do better than harm[28]. According to the decision curve analysis, patients with major LARS would have a net benefit superior to "treat all" or "treat none" with a range of threshold probability in ~20%-75% (Figure 3D).

External validation of the RF model

To assess the generalization capability of the RF model, an external validation based on 197 patients from another independent center was performed. The RF model identified patients with major LARS with an AUC of 0.852 (95%CI: 0.820-0.890) (Figure 4A). The confusion matrix presented the classification results generated by the RF model for identifying major LARS in the external validation set (Figure 4B). Figure 4C showed that the probabilities generated by the RF model for major LARS were significantly higher than those of no/minor LARS, suggesting that the predicted probabilities were significantly associated with the ground truth in the external validation set. Decision curve analysis also showed that patients would derive clinical benefits in a range of threshold probabilities (Figure 4D).

Evaluation of the prediction model

To assess the performance and calibration degree of the RF model in both the testing set and the external validation set, six performance metrics such as sensitivity, specificity, PPV, NPV, accuracy and Brier score were applied. Their results calculated based on the optimal Youden index (cut-off) were summarized in Table 2. These results suggested that the RF model was determined to be capable and reliable in predicting major LARS, with satisfactory Brier score of 0.152 and 0.166 and accuracy of 0.787 and 0.772, in both the testing set and the external validation set, respectively. In addition, to highlight the advantages of the RF model, the sensitivity, specificity, PPV, NPV and accuracy of the pre-operative LARS score (POLARS) model were calculated in both our testing set and external validation set. Taken together, these values demonstrate that the performance of the RF model surpassed that of the POLARS score model, as shown in Table 3.

DISCUSSION

LARS is the most common complication following rectal cancer surgery. It is a severe complication and seriously impairs patients' quality of life[1]. In a previous study, a meta-

analysis based on 11 studies indicated that the morbidity of major LARS was as high as 41% (95%CI: 34-48)[5]. Fortunately, surgeons are now paying more and more attention to the functional consequences of cancer treatment and the quality of life[1,4]. LARS is a time-dependent syndrome and the symptoms of some patients with LARS are relieved partly or completely one year or more after surgery. However, the symptoms in ~40% of patients remain stable and cannot be further improved[6,9,29]. Due to the variable symptom spectrum of LARS, ranging from incontinence for gas and liquid fecal matter to evacuation dysfunctions, and the complex etiology and unknown pathophysiology, there is no standard treatment available at present[30]. However, if patients with a high-risk major LARS can be treated with a conservative method (*e.g.*, pelvic floor rehabilitation, transanal irrigation) or minimally invasive therapies (*e.g.*, biofeedback therapy, sacral nerve stimulation) or multi-modal treatments during the period of the first year after surgery, their intestinal dysfunction may be significantly improved[9]. Consequently, the negative impact of LARS on their quality of life could be minimized. In addition, since major LARS may counteract the relative benefits of anal sphincter-preserving surgery, the accurate prediction of major LARS may be helpful for patients and surgeons when deciding on temporary ileostomy, permanent colostomy or sphincter-preserving surgery for low rectal cancer[31-33]. Therefore, it is crucial to perform risk stratification of rectal surgery cases to identify patients with a high risk of major LARS and to highlight patients who may require additional postoperative support.

Battersby *et al*[15] developed and validated the POLARS score for restorative sphincter-sparing surgery for rectal cancer to predict intestinal dysfunction. The POLARS score includes six risk factors, such as age at surgery, gender, tumor height, preoperative radiotherapy, total/partial mesorectal excision and the presence of stoma, as predictors. The model performs with moderate discriminative accuracy with Harrell's C statistic of 0.615 and 0.625 in their two datasets, respectively. Essangri *et al*[16] reported that the POLARS score was questionable and it failed to successfully validate the model in another population. This previous study implied that the model predictions may be dependent on patient background, including treatment strategies, physical, lifestyle and

dietary habit differences. In the present study, all participants were Chinese and underwent laparoscopic sphincter-sparing surgery for rectal cancer without splenic flexure mobilization. Several previous studies have pointed out that routine splenic flexure mobilization is not necessary for anterior resection of rectal cancer[34-36]. Instead, no splenic flexure mobilization would result in a shorter operation time and lower morbidity of postoperative complications associated with intestinal function, such as anastomotic leakage[37]. Moreover, to date, there is no machine learning model for predicting major LARS in Asian patients undergoing laparoscopic anterior resection based on a multicenter study.

In the present study, four machine learning algorithms were used to develop the machine learning model for major LARS prediction. These data suggested that the RF model performed with an optimal AUC in the training set. As expected, the RF model also achieved favorable predictions when it was tested in the testing and external validation sets. To the best of our knowledge, this is the first multicentric study to develop a machine-learning model for predicting major LARS in Asian patients undergoing laparoscopic anterior resection of rectal cancer. More importantly, the model performed with a satisfactory prediction in an independent medical center (AUC = 0.852; 95%CI: 0.820-0.890). Moreover, compared with the POLARS score, the RF model achieved superior performance in predicting major LARS in our cohort (accuracy of 0.772 for the RF model *vs* 0.355 for the POLARS score). In addition, the decision curve analysis demonstrates the net benefit (benefit minus risk) by using the model for patients diagnosed with major LARS within a range of threshold probabilities.

Although the explicit pathophysiological mechanism of LARS is still unclear, numerous studies[38-40] agree that intestinal dysfunction in patients with rectal cancer who received restorative sphincter-sparing surgery is the result of a combination of multiple pathophysiological mechanisms. These include loss of rectal storage function, autonomic denervation, enhanced colonic movement, rectal-anus sensitivity reduction, anal resting pressure reduction and diverting colitis[38]. Certain factors directly or indirectly related to these pathophysiological changes have been reported as important variables associated

with LARS, such as low anastomosis, neoadjuvant therapy, postoperative chemoradiotherapy, anastomotic leakage, diverting stoma and the time interval from the creation of diverting stoma to closure[5,18,41,42]. In order to identify major LARS in the early postoperative period, some postoperative factors were not included, such as chemoradiotherapy and the time interval from creating diverting stoma to its closure. Among the included factors, low anastomosis and neoadjuvant therapy have been unanimously considered as important predictors for major LARS[5,43]. For example, Filips et al[44] reported that LARS was negatively correlated with the distance from anastomosis to the anal verge (OR: -1.145, 95%CI: -2.149 to -1.141, P = 0.026). In the present study, our data also indicated that the anastomotic height was the most important factor in the development of major LARS. What's more, the specimen length was selected as a predictor for major LARS in the present study, and it may be caused by greater surgical trauma.

As with any retrospective observational study, the present study had some uncontrollable limitations. First, the model is based on the Chinese population and does not necessarily reflect the worldwide target population, and its generalization ability needs to be further tested. Second, the influence of a patient's socioeconomic and cultural background, self-management ability and social support are difficult to control. Third, the data reflecting anal sphincter injury and its severity during surgery cannot be evaluated. Finally, the LARS score may be affected by a variety of biases, such as patient selective memory, exaggeration or understatement. To overcome these limitations, a prospective study is proposed to assess the predictive ability of the model.

CONCLUSION

In the present study, a machine learning model based on preoperative and intraoperative risk factors for predicting LARS was developed. The model may be helpful for clinical medical staff to identify patients at an early stage with a high risk of developing major LARS within one year following laparoscopic surgery for rectal cancer. Moreover, it can

potentially also be used for patients to acquire early postoperative consultation and strengthen self-management to improve patients' quality of life.

ARTICLE HIGHLIGHTS

Research background

Low anterior resection syndrome (LARS) severely impairs patient postoperative quality of life, especially major LARS. However, there are few tools that can accurately predict major LARS in clinical practice.

Research motivation

To stratify patients with LARS and predict patients at high risk of developing major LARS, improve patient counseling, and highlight patients who may need additional support after surgery.

Research objectives

The study aimed to identify the risk factors associated with major LARS and develop a prediction model that helped improve patient counseling and highlight patients who may need additional support after surgery.

Research methods

Clinical data and follow-up information of patients from two medical centers (one discovery cohort and one external validation cohort) were analyzed to identify independent factors associated with major LARS. For the discovery cohort, the machine learning prediction algorithms were developed and internally validated, and in the external validation cohort, we evaluated the trained model using various performance metrics. Further, the clinical utility of the model was tested by decision curve analysis.

Research results

Eight factors, such as anastomotic height, neoadjuvant therapy, diverting stoma, body mass index, clinical stage, specimen length, tumor size and age, were selected as significantly relevant to major LARS. A machine learning-based prediction model that integrated eight risk factors as input features was developed, externally validated, and demonstrated acceptable predictive performance.

Research conclusions

We have developed and validated a robust tool for predicting major LARS. This model could potentially be used in the clinic to identify patients with a high risk of developing major LARS and then improve their quality of life.

Research perspectives

A prospective study including more medical centers would be proposed to assess the model's predictive ability.

84049_Auto_EditedC.docx

ORIGINALITY REPORT

24%

SIMILARITY INDEX

PRIMARY SOURCES

1   Shengli Shao, Yufeng Zhao, Qiyi Lu, Lu Liu, Lei Mu, Jichao Qin. "Artificial intelligence assists surgeons' decision-making of temporary ileostomy in patients with rectal cancer who have received anterior resection", European Journal of Surgical Oncology, 2022
    Crossref
    147 words — 4%

2   www.ncbi.nlm.nih.gov
    Internet
    129 words — 3%

3   doctorpenguin.com
    Internet
    116 words — 3%

4   www.frontiersin.org
    Internet
    45 words — 1%

5   Ming Jun Huang, Lin Ye, Ke Xin Yu, Jing Liu, Ka Li, Xiao Dong Wang, Ji Ping Li. "Development of prediction model of low anterior resection syndrome for colorectal cancer patients after surgery based on machine‐learning technique", Cancer Medicine, 2022
    Crossref
    42 words — 1%

6   www.wjgnet.com
    Internet
    41 words — 1%

7   bmcneurol.biomedcentral.com
    Internet
    38 words — 1%

8   www.accjournal.org
Internet

35 words — 1%

9   link.springer.com
Internet

34 words — 1%

10   Lin Ye, MingJun Huang, YuWei Huang, KeXin Yu, XiaoDong Wang. "Risk factors of postoperative low anterior resection syndrome for colorectal cancer: A meta-analysis", Asian Journal of Surgery, 2021
Crossref

24 words — 1%

11   oriprobe.com
Internet

22 words — 1%

12   academic-accelerator.com
Internet

20 words — < 1%

13   worldwidescience.org
Internet

17 words — < 1%

14   journals.plos.org
Internet

16 words — < 1%

15   rcastoragev2.blob.core.windows.net
Internet

16 words — < 1%

16   Qiyuan Qin, Binjie Huang, Wuteng Cao, Jie Zhou, Tenghui Ma, Zhiyang Zhou, Jianping Wang, Lei Wang. "Bowel Dysfunction After Low Anterior Resection With Neoadjuvant Chemoradiotherapy or Chemotherapy Alone for Rectal Cancer: A Cross-Sectional Study from China", Diseases of the Colon & Rectum, 2017
Crossref

15 words — < 1%

17   Mahamed Lamine Guindo, Muhammad Hilal Kabir, Rongqin Chen, Fei Liu. "Potential of Vis-NIR

14 words — < 1%

to measure heavy metals in different varieties of organic-fertilizers using Boruta and deep belief network", Ecotoxicology and Environmental Safety, 2021
Crossref

18   f6publishing.blob.core.windows.net
      Internet   13 words — < 1%

19   Modern Management of Cancer of the Rectum,
      2015.   12 words — < 1%
      Crossref

20   Xuan Zou, Yong Wei, Tao Qi, Xiaping Wang,
      Wenren Zuo, Tongshan Wang, Wei Zhu, Xin Zhou.   12 words — < 1%
      "A novel 6-gene signature derived from tumor-infiltrating T cells
      and neutrophils predicts survival of bladder urothelial
      carcinoma", Aging, 2021
      Crossref

21   ir.ymlib.yonsei.ac.kr
      Internet   12 words — < 1%

22   www.nature.com
      Internet   12 words — < 1%

23   D. J. Brennan. "Routine Mobilization of the Splenic
      Flexure is not Necessary During Anterior   11 words — < 1%
      Resection for Rectal Cancer", Diseases of the Colon & Rectum,
      03/2007
      Crossref

24   Kenji Ueki, Akihiro Tsuchimoto, Yuta Matsukuma,
      Kaneyasu Nakagawa et al. "Development and   11 words — < 1%
      validation of a risk score for the prediction of cardiovascular
      disease in living donor kidney transplant recipients",
      Nephrology Dialysis Transplantation, 2021
      Crossref

25 static.frontiersin.org
    Internet   11 words — < 1%

26 Tomomitsu Tahara, Takuya Shijimaya, Shuhei
    Nishimon, Yasushi Matsumoto et al. "Sa1073:   9 words — < 1%
    PREDICTION OF INVASION DEPTH OF SUPERFICIAL
    ESOPHAGEAL SQUAMOUS CELL CARCINOMA COMBINING
    MAGNIFYING NBI INTRAPAPILLARY CAPILLARY LOOP
    CLASSIFICATION AND WALL DEFORMITY BY NON-MAGNIFYING
    CONVENTIONAL ENDOSCOPY", Gastroenterology, 2022
    Crossref

27 mdpi-res.com
    Internet   9 words — < 1%

28 www.researchgate.net
    Internet   9 words — < 1%

29 www.science.gov
    Internet   9 words — < 1%

30 Cynthia A. Wong, Robert J. Fragen, Paul C.
    Fitzgerald, Robert J. McCarthy. "The Association   8 words — < 1%
    Between Propofol-Induced Loss of Consciousness and the
    SNAP??? Index", Anesthesia & Analgesia, 2005
    Crossref

31 Daonan Chen, Rui Wang, Yihan Jiang, Zijian Xing,
    Xiaoqing Liu, Lina Zhao, Hui Xie. "Application of   8 words — < 1%
    Artificial Neural Network in Daily Prediction of Bleeding in ICU
    Patients Treated With Anti-Thrombotic Therapy", Research
    Square Platform LLC, 2023
    Crossref Posted Content

32 Li Yang, Jing Ma, Wei Zhou, Lei Sun et al. "Ultrafast
    Preliminary Screening of COVID-19 by Machine   8 words — < 1%

Learning Analysis of Exhaled NO", Research Square Platform LLC, 2020
Crossref Posted Content

33 M. van Heinsbergen, J. A. G. Van der Heijden, L. P. Stassen, J. Melenhorst et al. "The low anterior resection syndrome in a reference population: prevalence and predictive factors in the Netherlands", Colorectal Disease, 2019
Crossref

8 words — < 1%

34 Sayaka Shinohara, Yuan-Hsin Lin, Hirofumi Michimae, Takeshi Emura. "Dynamic lifetime prediction using a Weibull-based bivariate failure time model: a meta-analysis of individual-patient data", Communications in Statistics - Simulation and Computation, 2020
Crossref

8 words — < 1%

35 assets.researchsquare.com
Internet

8 words — < 1%

36 hdl.handle.net
Internet

8 words — < 1%

37 ousar.lib.okayama-u.ac.jp
Internet

8 words — < 1%

38 David G. Jayne, Pierre J. Guillou, Helen Thorpe, Philip Quirke et al. "Randomized Trial of Laparoscopic-Assisted Resection of Colorectal Carcinoma: 3-Year Results of the UK MRC CLASICC Trial Group", Journal of Clinical Oncology, 2007
Crossref

7 words — < 1%

EXCLUDE QUOTES   OFF   EXCLUDE SOURCES   OFF
EXCLUDE BIBLIOGRAPHY   OFF   EXCLUDE MATCHES   OFF