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Research Article

The artificial neural network (ANN) system for prediction of improving outcomes in UUTC (upper urinary tract tumor) patients treated with ERAS (Enhanced recovery after surgery)

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Running Title: ANN system for prediction of improving outcomes in UUTC with ERAS

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ABSTRACT

Objective: To explore the clinic value of ERAS (enhanced recovery after surgery) in postoperative recovery (laparoscopic surgery) for curative treatment on UUTC (upper urinary tract tumor), and predict the outcomes with an artificial neural network (ANN) system. **Methods:** After laparoscopic surgery for curative treatment on UUTC, patients were randomly assigned to the two groups ERAS and control group, the perioperative and postoperative short-term outcomes were compared. Clinical characteristics, handing methods, and clinical outcomes data were analyzed using an adapted ANN model. The strength of the ANN prediction was measured between -1 and 1 with -1 representing bad outcome and 1 representing good outcome. **Results:** In ERAS group, postoperative exhaust and defecation time, as well as the time of beginning taking food or off bed activities for patients were shorter obviously than control. Moreover, the length of hospital stay and post-operative pain in ERAS patients were obviously less than in control group. The ANN applied here was able to accurately predict all patients outcomes.

Conclusions: ERAS could improve postoperative recovery after laparoscopic surgery for the curative treatment of UUTC. ERAS value nodes can be applied to a simple AAN model to accurately predict outcome of patients with UUTC treated with ERAS.

Keywords: artifical neural network (ANN); enhanced recovery after surgery (ERAS); laparoscopic surgery; curative treatment; upper urinary tract tumor (UTCC)

INTRODUCTION

A series of papers had been published by Kehlet et al. in the late 1990s, it was about colorectal surgery involved in fast-track multimodal programme. It could shorten the LOS (length of stay) and reduce complications [1-3]. Consequently, ERAS (Enhanced Recovery after Surgery) was evolved into a commonly multidisciplinary instrument in this notion. It integrates a few of elements about perioperative, and now it is well known that the protocol of ERAS. In recent year, a lot of official guidelines were published from Society of ERAS. Moreover, a few of meta-analyses investigation indicated the benefits of ERAS through comprising other surgical disciplines [4-6]. The philosophy of ERAS involved in multidisciplinary team of physiotherapists, dieticians, nurses, anaesthetists, and surgeons. All they want to facilitate care quality through shifting knowledge based on evidence into practice of clinic [7].

Therefore, the value of ERAS programmes on useful evidence in laparoscopic surgery for UUTC (upper urinary tract tumor) is sparse. Moreover, there are limited benefits of modern multimodal perioperative care and no official guidelines of ERAS come from documenting papers. Nonetheless, it has been suggested that the majority of general principles used in laparoscopic surgery may be applicable [8-10]. But, there are a number of published reports demonstrated that was widely used of its elements of perioperative in other types of surgery. However, the unified protocol of laparoscopic surgery, especially for the curative treatment of upper urinary tract tumor has been not indicated.

Artificial neural networks (ANN) represent forms of artificial intelligence that simulate intelligent behavior by mimicking the way that biologically generated neural networks function [11]. An ANN utilizes simple artificial nodes known as “neurons”, and connects them to form an array of different “synaptic” networks. The networks are then trained with established data to strengthen or weaken different nodal connections that favor recognizable network patterns of connectivity. Data is aggregated in one or more intermediate weighted progressions known as “hidden layers” before possible outcomes are compared to generate an output or “decision”. Similar characteristics that tend to cluster in association with specific outcomes form the basis of probability weighting for future events. During a teaching phase where both input criteria and known output values are entered, an error value is established as deviance from known outputs with similar inputs. Weighting is adjusted recursively during training until output error approximates established error. For new data, each node in the hidden layer summates the weighted input values and generates a new weight before aggregating into a predicted outcome. The key characteristic of a neural network is its ability to learn as it recognizes more unique correlations/associations to predict more reliable outcomes.

UUTC, and improves postoperative recovery (laparoscopic surgery) with ERAS is a complex and poorly understood topic which lends itself ideally to the application of ANNs. ANNs are good decision making tools in situations where complex data are not amenable to the development of simple rules or algorithms. Since ANNs require adequate high quality teaching data where outcomes are known, and teaching data sets cannot be used as testing data, a substantial volume of clinical cases are needed to establish a new ANN. Since there is a paucity of UUTC, and improves postoperative recovery (laparoscopic surgery) with ERAS based on good clinical and angiographic data, we tested an established ANN trained with UUTC, and improves postoperative recovery (laparoscopic surgery) with ERAS data value nodes exclusive of clinical characteristics, handing methods, and clinical outcomes data, etc., to see if it might be applicable to our clinical data set with known outcomes in UTCC patients treated with ERAS.

This work want to evaluate systematically and perform a prospective random control study of the available evidence on pathways of ERAS compared to traditional care in perioperative patients treated with laparoscopic surgery for the curative treatment on UUTC, and predict outcome with ANN.

MATERIALS AND METHODS

Participant recruitment and selection criteria

Inclusion criteria:

(1) These patients were 45-78 years old; (2) had a diagnosis of upper urinary tract tumor, such as kidney cancer, carcinoma of the renal pelvis or the ureter; (3) were performed laparoscopic surgery for the curative treatment of tumors; (4) were without serious complications of heart, lung, brain or metabolic disease.

Excluding criteria:

(1) There were damage of other viscera, and receipt of blood transfusion or conversion to laparotomy; (2) had a history of abdominal or chest surgery; (3) with primary disease of heart, lung, brain, liver, or kidney, primary diabetes, abnormal glucose tolerance, severe obesity (body mass index-BMI > 30 kg/m^2) , or severe malnutrition (BMI < 15 kg/m^2).

According to the above criteria, a total of 148 patients after laparoscopic surgery for the curative treatment of upper urinary tract tumor were included in this analysis, and assigned to the ERAS group (80 cases) and control group (68 patients treated with traditional protocols) at random from January, 2015 to December, 2017. The perioperative and postoperative short-term outcomes were compared between the two groups. The clinical characteristics, such as gender, age, body mass index (BMI), operation method, operation time, intraoperative blood loss, and tumor stage were compared between the two groups, as shown in Table 1.

This study was approved by the Ethics Committee of People’s Hospital of Jilin Province according to the Declaration of Helsinki. The use of patients’ documents in this research was approved by the Ethics Committee of People’s Hospital of Jilin Province according to the Declaration of Helsinki. And we clearly confirm that we had consents from any patients. We had record and document participant consent in People’s Hospital of Jilin Province. And the ethics committees of People’s Hospital of Jilin

Province hospital had approved this consent procedure.

Observable indicators

The perioperative and postoperative short-term outcomes were compared between the two groups, including postoperative exhaust and defecation time, as well as the time of beginning taking food or off bed activities for patients, and length of hospital stay (Table 3).

VAS (visual analogue scale) was used to evaluate the pain at the admission, or assess the post-operative pain at 2 h, 12 h, 24 h, and 48 h while patients were fully awake following surgical anesthesia (Table 4).

Follow-up of the data evaluation

The routine clinic follow-up was performed in this study every 4 weeks during the first 6 months after surgery. Blood or urine routine, liver and kidney function, abdominal CT and cystoscopy were re-exminationed for all patients. Other test items were determined according to the judgment of clinician. The mainly vital signs and symptoms of patients, including food intake, appetite, the change of BMI, the status of abdominal distention and pain or urine.

ANN model

The ANN modeling utilized in this study was adapted from Dumont and was built with a commercially available program [11-13]. Twenty-six variables spanning clinical characteristics (10 items, Table 1), handing methods (10 items, Table 2), and clinical outcome data (6 items, Table 3-5) utilized by this ANN served as predictors for improving postoperative outcomes of UUTC with ERAS. The prediction of ERAS was presented by the ANN as a scaled value where outputs greater than 0 predicted in favor of ERAS and values less than 0 predicted the absence of ERAS.

The single time-point ANN model presented in this study, also called a binary classification ANN, is essentially a logistic regression analogue for binary classification tasks. In a binary classification problem, an input pattern is classified into 1 of the 2 nonoverlapped classes, say *C*1 and *C*2. The decision is based on estimating the conditional probability of observing an individual with class level *C*1 given a set of covariate values [14]. In a linear logistic regression model, a single target variable Y is defined such that Y =1 denotes class *C*1 and Y =0 denotes class *C*2.

Let $p(x) = P(Y = 1|X = x)$, the logistic regression model is expressed as follows:

$$p(x)=\frac{\exp(\beta 0+\beta x)}{1+\exp(\beta 0+\beta x)}+\frac{1}{1+\exp(\beta 0+\beta x)}$$

Equivalently, the log odds, called the logit, show the linear relationship as follows:

$$\text{logit}\left[p(x)\right]=\log\frac{p(x)}{1-p(x)}=\beta_0+\beta_x,$$

where the unknown parameters β are called the ‘regression coefficients’ and are estimated using the maximum likelihood procedure. This equates the logit link function to the linear predictor. To minimise the misclassification rate, we should predict Y =1 when P□.5 and Y =0 when P <.5. The network is set up in 3 interconnected layers: an input layer with nodes corresponding to the prognostic covariates, a hidden layer for modelling nonlinearity, and a single output layer that represents survival at a certain time point. The network is composed of p input units, H hidden units, and 1 output unit. The units in the input layer $\Lambda(u) = 1/(1 + \exp(-u))$ correspond to prognostic covariates. Each unit in the hidden layer estimates a weighted sum of the input variables and the bias. By selecting a common activation function Λ for the hidden units, the output of the hidden unit h is given by

$$0h = \Lambda(\omega 0h + \sum_{i=1}^{p} \omega ihxi) i = 1, \ldots, p, h = 1, H,$$

where ω_{ih} is the weight from input *i* to the hidden unit *h* and ω_{0h} is the bias for the hidden unit *h*, *h*=1, ...,*H*.

Statistical analysis

Data analysis was carried out using SPSS 18.0 software (Inc. Chicago, SPSS, IL). The demographic data and disease characteristics of patients were compared between the two groups. The qualitative data was showed as frequency and rates. The quantitative data was analyzed using *t*-test, and the differences between the two groups were analyzed with chi square test or Fisher test. P<0.05 was considered statistically significant.

RESULTS

Clinical characteristics

The clinical data of age, gender distribution, BMI, operation method or time, ASA grade, the location or stage of tumor, intraoperative blood loss etc. were not statistically different between the two groups (P>0.05) (Table 1).

Handing methods

The patients and their family in ERAS group received the education intervention (face to face and booklet) before operation, but not in control group. The health education included the operation plan and the details of ERAS program. Additionally, these patients were assisted with the use of postoperative guidance for early off bed activities. The different handing methods were conducted in the two groups, and shown in Table 2.

Perioperative and postoperative short-term outcomes

The perioperative and postoperative short-term outcomes were compared between the two groups. In ERAS group, postoperative exhaust and defecation time, as well as the time of beginning taking food or off bed activities for patients were significantly shorter than control group (Table 3).

VAS (visual analogue scale) and degree of pain

VAS (visual analogue scale) was used to evaluate the pain at the admission, or assessed the post-operative pain at 2 h after fully awake following surgical anesthesia, and 12 h, 24 h, and 48 h after surgery (Table 4). Our results showed that, in ERAS group, the VAS at each observable time were significantly lower than control group (Table 4). Moreover, patients without or with mild pain in ERAS group were obviously more than that in control group (P=0.001, Table 5). Additionally, patients with moderate or severe pain in ERAS group were obviously less than that in control group (P=0.001, Table 5).

The predict outcome with ANN

Twenty-six input variables were applied in the ANN. All outcomes of patients were correctly predicted by the ANN. The mean strength of prediction for those who did not exhibit SCV was -0.89, (where-1 represented bad outcome and 1 represents good outcome). The prediction strength for the one patient in this cohort who had good outcome was 0.92.

DISCUSSION

The preoperative treatment with ERAS, it is mean that health, painless, individualized education, which can make patients relief, reduce the fear of surgery, especially the fear of pain [15]. ERAS advocated simple intestinal preoperative preparation, such as oral lactulose, promote natural defecation of patients. Moreover, the simple intestinal preparation does not increase the risk for postoperative intestinal infection and prolonging the postoperative defecation time. Additionally, patients were more likely to accept ERAS, because of which could reduce fear and nervousness come from surgery. But, traditional mechanical bowel prepare before operation cause fluid loss and electrolyte disorder [15], and that increase fear and blood pressure fluctuations of patients.

In addition, the rule of traditional perioperative management thought patients should receipt deprivation of fasting and water for 12 h before operation, and just can eat after postoperative while thoroughly recovery of gastrointestinal function. But many studies have shown that preoperative oral carbohydrate and a moderate amount of warm water can prevent hypoglycemia in operation. Moreover, it reduce the risk of insulin resistance, and improve patients to feel comfortable, promote restoration of intestinal peristalsis and exhaust [16]. In this research, the patients of ERAS group receipt free fasting in normal at the night before surgery, but have 12.5% carbonated drink for 500 ml at 9 pm and oral warm sugar water (warm water for patient with Diabetes) 300 ml at 6 am in the morning of surgery day. A piece of chewing gum was administered after awake anesthesia, which stimulate production of saliva. Our results indicated that the time of postoperative anal exhaust, feeding, and off bed activities in patients of ERAS group was all earlier than those of conventional group ($P<0.05$). Moreover, the postoperative complications in ERAS group were lower than control group, which is consistent with the literatures reported [17].

About intraoperative treatment of ERAS, ERAS advocates the minimally invasive surgery, accurate operation, but especially pay attention to the protection of temperature intraoperative, restricted the amount of fluids and the application of a short-acting anesthetic drugs. Some researchers identified that intraoperative low body temperature rise 2-3 times in incidence of wound infections, and lead to a marked increase in the incidence of arrhythmia, etc, and even abnormal coagulant function. However, the intraoperative preservation of body temperature can reduce the postoperative stress reaction, which is beneficial to reduce the body catabolism and promote recovery of patients [18]. Intraoperative excess fluids and blood transfusion can cause cardiac insufficiency or peripheral tissue edema, and increase the formation of postoperative thoracic and abdominal cavity effusion [19]. Excessive application of long-short acting anaesthetic drugs is not conducive to patients with rapid awakening and recovery at an early date after surgery, even cause auditory and visual hallucination in some patients.

The postoperative treatment of ERAS is an important link in course of ERAS [20], adequate analgesia can effectively reduce stress of patients, promote early ambulation and recovery of gastrointestinal function, prevent formation of deep vein thrombosis in lower limbs and complications such as atelectasis, pulmonary infection, shorten the length of hospital stay, and reduce hospitalization expenses. In this work, the combined method of analgesia was adopted, ropivacaine was subcutaneous injected around the wound at the end of surgery, and intravenous injection unselective inhibitor of COX-2, Liposomal Flurbiprofen Axetil (50mg) at 6 h, 18 h, and 30 h after surgery. Our results showed that, in ERAS group, the VAS at each observable time were significantly lower than control group (Table 4). Moreover, patients without or with mild pain in ERAS group were obviously more than that in control group (*P*=0.001, Table 5). Additionally, patients with moderate or severe pain in ERAS group were obviously less than that in control group (*P*=0.001, Table 5). It is shown that the combined analgesia scheme brought patients satisfactory analgesia effect, and make the patients get better rest, provides favorable conditions for early postoperative ambulation. Early postoperative off bed was also advocated by the traditional idea in nursing, but as a result of inadequate postoperative analgesia, off bed of patients is restricted in the subjective and objective, which lead to bad patient compliance. In this study, on the basis of effective analgesia for patients, medical staff gave effective education about the benefits of early postoperative ambulation, so relieve patients' anxiety and fear of negative emotions. Therefore, positive cooperation was obtained, then the compliance of postoperative off bed activities were improved, then it speeded up the process of recover. The concept of ERAS of perioperative nursing has played a very positive role.

The retention of drainage tube increases the patient's pain, and limit the patient's subjective activity, influence the intestinal peristalsis, also increases the chance of infection [21-24]. Hence, ERAS advocate a reduction the number and the time of retention of drainage tube, which will decrease the pain feeling of patients, and be easily to their early actively movement and diet, furthermore, accelerate rehabilitation process, also improve patient satisfaction of operation.

This study proposes a single time-point ANN approach that can predict the outcome of patients at any predetermined points of time. A single time-point ANN model is efficient when prognosis is of interest at a specified time point. For example, in cancer studies, the outcome is generally reported within 5 years of treatment. In public health studies involving the development of certain diseases or conditions, the event occurrence is generally observed within 10 years [14]. In such cases, a neural network structure can be developed for producing the outcome estimates at specific follow-up times. The proposed single time-point ANN approach has the advantage that no temporal structure such as proportional hazards is assumed in the model, which allows for flexible prediction modelling of outcome. The single time-point ANN model presented in this study, also called a binary classification ANN, is essentially a logistic regression analogue for binary classification tasks. Considering many diseases, the prediction of the probable outcome of patients can be a challenging objective [25]. For different types of cancer, the estimated risk of the patient can directly affect the choice of treatment. However, some investigations usually aim only at finding the relative importance of the prognostic factors or comparing the performance of ANN models with the conventional analysis methods; little effort has been put to apply the ANN methodology to censored data modelling. This study focuses on developing an efficient ANN structure with the ability to handle censored data. The single time-point feed-forward ANN models were developed for predicting the outcome for UTCC patients treated with ERAS after surgery.

In conclusions, enhanced recovery after laparoscopic surgery used in perioperative management for the curative treatment of upper urinary tract tumor is safe and effective, it can improve postoperative recovery process in ERAS group patients, shorten the length of hospital stay, and then reduce hospitalization expenses. The successfully implemented ideas about ERAS are the common effort of multidisciplinary collaboration, including medical, nursing, anesthesia, etc., each link closely connect to each other, but none is dispensable. Moreover, the scientific understanding of clinicians to ERAS is the most critical, we hope that with the development of the surgery, the multidisciplinary communication increase gradually, more and more doctors could realize the scientific nature of ERAS and its advancement, and then early apply its clinical benefit to more patients. This study demonstrates the feasibility of applying ANN models in medical decision support systems that use clinical data sets for predicting the outcome of patients with UTCC dealt with ERAS after surgery. The clinical application of the proposed ANN prediction models can potentially improve prognosis accuracy and treatment decisions for the patients. The development of better clinical decision support systems for UTCC with ERAS prognosis could decrease uncertainty in prognosis, thus allowing treatment to be focused on patients with the worst expected survival chances.

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Table 1 Compare clinical characteristics between the two groups.

Clinical characteristics	ERAS group (n=80)	Control group (n=68)	*Statistic value*	*P* value
Age ($\bar{x}$ ±s)	64.94±5.45	63.51±6.27	t=1.46	0.445
Gender (Male/Female)	34/46	31/37	χ^2=0.142	0.706
BMI (kg/m^2, $\bar{x}$ ±s)	20.4±2.1	19.8±2.7	t=1.49	0.248
ASA grade [n (%)]				
I	14 (17.5)	19 (27.9)	χ^2=2.313	0.128
II	45 (56.25)	36 (52.9)	χ^2=0.162	0.687
III	21 (26.25)	13 (19.1)	χ^2=1.057	0.304
Operation method [n (%)]			χ^2=0.03	0.862
Kidney cancer [n (%)]	59 (73.75)	51 (75)		
Carcinoma of the renal pelvis or the ureter [n (%)]	21 (26.25)	17 (25)		
Operation time (min)	133.2±35.8	141.8±30.7	t=1.57	0.412
Intraoperative blood loss (ml)	108.6±55.1	127.2±69.8	t=1.78	0.256
Tumor stage [n (%)]				
T1	7	5	χ^2=0.096	0.756
T2	62	49	χ^2=0.58	0.446
T3	11	14	χ^2=1.224	0.269

Note: ASA, American Society of Anesthesiologists.

Table 2 Compare handing methods between the two groups in perioperative period.

Handing methods	ERAS group (n=80)	Control group (n=68)
Before operation		
Health education	Received the education intervention	None
Gastrointestinal preparation	Free fasting in normal at the night before surgery, but have 12.5% carbonated drink for 500 ml at 9 pm; oral warm sugar water (warm water for patient with Diabetes) 300 ml at 6 am in the morning of surgery day	Deprivation of fasting and water for 12 h
Mechanical bowel preparation	Oral lactulose to promote natural defecation in the afternoon (3 pm) before surgery	Enema at the night before surgery
In operation		
Anesthetization	Received general anesthetization with short-acting anesthetic, and using infusion and transfusion as little as possible	Routine

Heat preservation	Keep body temperature of patient as soon as possible with insulation measure	No intervention
Drainage tube	Using latex tube as little as possible, remove at 1-3 d after surgery	Using silicone tube, remove at 5-8 d after surgery
After operation		
Analgesic methods	Subcutaneous injection of ropivacaine at the end of surgery, and intravenous injection unselective inhibitor of COX-2, Liposomal Flurbiprofen Axetil (50mg) at 6 h, 18 h, and 30 h after surgery	Intramuscular short-acting paregoric Dolantin or patient controlled intravenous analgesia (PCIA)
Catheter	Retention catheterization in operation, remove at 1-4 d after surgery	Retention catheterization before operation, remove at 5-7 d after surgery
Off bed activities early	Encourage off bed activities at 1 d after surgery	Encourage off bed at 4-6 d after surgery
Diet	With lipid at 1 d after surgery	With lipid post-surgery anal-exsufflation

Table 3 Compare postoperative short-term outcomes between the two groups.

Postoperative short-term outcomes	ERAS group (n=80)	Control group (n=68)	*t* value	*P* value
The time of the first post-surgery anal-exsufflation (h, $\bar{x}$ ±s)	28.1±3.45	36.5±5.24	11.67	0.012
The time of post-surgery infusion (h, $\bar{x}$ ±s)	30.3±2.19	48.4±4.12	32.3566	0.004
The time of the first post-surgery off bed activities (h, $\bar{x}$ ±s)	21.6±2.46	54.2±5.38	46.03	0.001
Length of hospital stay (d, $\bar{x}$ ±s)	5.2±1.26	8.6±2.77	9.338	0.031

Table 4 Compare VAS (visual analogue scale) between the two groups.

VAS (visual analogue scale) (score, $\bar{x}$ ±s)	ERAS group (n=80)	Control group (n=68)	*t* value	*P* value
2 h after fully awake following surgical anesthesia	3.86±1.45	4.91±1.31	4.587	0.031
12 h after surgery	4.05±1.39	5.64±1.63	6.417	0.036
24 h after surgery	4.15±1.52	6.32±1.78	8.002	0.042
48 h after surgery	4.21±1.64	5.83±1.21	6.7348	0.034
The time of the first post-surgery off bed activities	4.69±1.27	6.57±1.54	8.14	0.037

Table 5 Compare the degree of pain between the two groups after surgery.

The degree of pain	ERAS group (n=80, %)	Control group (n=68, %)	χ^2 value	*P* value
None	22 (27.5)	2 (2.9)	16.31	0.001
Mild	49 (61.2)	6 (8.8)	43.26	0.001
Moderate	9 (11.3)	38 (57.4)	33.78	0.001
Severe	0	22 (30.9)	30.40	0.001