Surgical Oncology 28 (2019) 128–134

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

The prognostic value of a Surgical Outcome Risk Tool in patients after radical gastrectomy for gastric cancer and its guiding significance for postoperative chemotherapy

Ru-Hong Tu[a,b], Jian-Xian Lin[a,b], Ping Li[a,b], Jian-Wei Xie[a,b], Jia-Bin Wang[a,b], Jun Lu[a,b], Qi-Yue Chen[a,b], Long-long Cao[a,b], Mi Lin[a,b], Chao-Hui Zheng[a,b,c,d,**], Chang-Ming Huang[a,b,c,d,*]

[a] Department of Gastric Surgery, Fujian Medical University Union Hospital, Fuzhou, China
[b] Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, China
[c] Key Laboratory of Ministry of Education of Gastrointestinal Cancer, Fujian Medical University, Fuzhou, China
[d] Fujian Key Laboratory of Tumor Microbiology, Fujian Medical University, Fuzhou, China

ARTICLE INFO

Keywords:
Stomach cancer
Risk stratification
Prognosis

ABSTRACT

Objective: To provide individualized survival predictors for patients after radical gastrectomy and to guide adjuvant treatment.

Methods: The data of patients with gastric cancer treated in our department from January 1996 to December 2014 were analyzed retrospectively. A Surgical Outcome Risk Tool (SORT) was used to indicate the physical condition of the patients.

Results: A total of 5327 patients in the study. The 5-year overall survival rates in the low-, moderate- and high-risk group were 61.6%, 54.7% and 44.4%, respectively ($p < 0.001$). A multivariate analysis showed that SORT was an independent prognostic factor for gastric cancer. There was significant chemotherapy benefit after surgery in stage II-III patients with a SORT < 3 and in stage III patients with a SORT ≥ 3 ($p < 0.05$). However, chemotherapy did not improve the 5-year overall survival in stage II patients with a SORT ≥ 3 (62.4% vs. 48.3%, $p = 0.196$). The calculated difference between two nomogram models was the potential benefit of adjuvant chemotherapy for patients with gastric cancer.

Conclusion: A SORT is an independent risk factor for predicting the prognosis of gastric cancer, and postoperative adjuvant chemotherapy should be carefully adopted in stage II patients with a SORT ≥ 3.

1. Introduction

Gastric cancer is one of the most important diseases threatening human health. Surgical resection, as the only possible radical treatment for gastric cancer, has attracted the attention of scholars [1]. Specifically, for patients undergoing radical resection, how to maximize the effectiveness of oncology has been the focus of attention among scholars. And scholars made great progress in the field of neoadjuvant chemoradiotherapy, lymph node dissection, adjuvant chemoradiotherapy, molecular targeted therapy, etc. [2–6] However, the long-term survival for patients with gastric cancer is directly related to the TNM stage of the tumor and is inevitably affected by the high-risk factors of the patient's own presence [7]. We hypothesize that a patient with a poor physical condition may lead to a reduction in their overall survival when compared with another patient in the same stage but in a better physical condition. And the benefit of adjuvant chemotherapy may outweigh the disadvantages for the patients with a poor physical condition. But before answering these questions, it is necessary to quantify the risk factors of the patient's own condition. Scholars have built a number of objective and rigorous risk assessment systems, such as SORT, ASA-PS, SRS, and POSSUM [8–11]. Considering that other scoring systems may be too simple or complex, their prediction accuracies might not be high and their application might not be wide enough [12]. Thus, in the present study, we used a SORT surgical risk assessment system for further evaluation. The system effectively quantified the high-risk factors of patients and provided an objective and effective tool for studying the patient's self-status on prognosis [8,13]. Therefore, this study aimed to assess the patient's status, to

* Corresponding author. Department of Gastric Surgery, Fujian Medical University Union Hospital, No.29 Xinquan Road, Fuzhou, 350001, Fujian Province, China.
** Corresponding author. Department of Gastric Surgery, Fujian Medical University Union Hospital, No.29 Xinquan Road, Fuzhou, 350001, Fujian Province, China.
E-mail addresses: wwkzch@163.com (C.-H. Zheng), hcmlr2002@163.com (C.-M. Huang).

https://doi.org/10.1016/j.suronc.2018.11.008
Received 17 June 2018; Received in revised form 18 October 2018; Accepted 8 November 2018

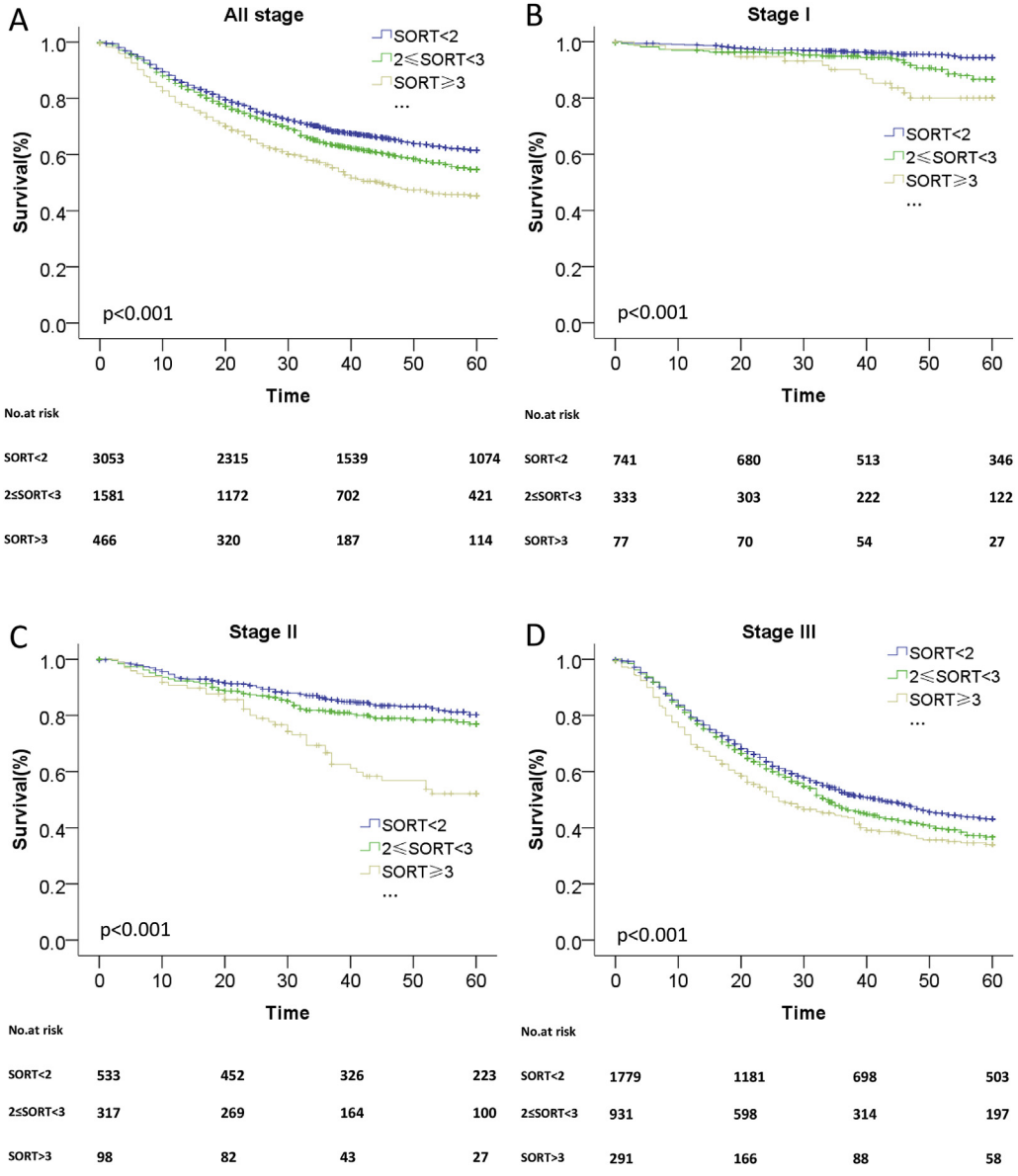

Fig. 1. Kaplan-Meier curves of patients in different SORT groups. (A) Overall survival in all patients, (B) overall survival in pStage I patients, (C) overall survival in pStage II patients, (D) overall survival in pStage III patients.

provide individualized survival predictors for patients after radical gastrectomy and to guide the choice of adjuvant treatment.

2. Methods

2.1. General information

A retrospective analysis was carried out by including patients with primary gastric cancer who had received radical resection of gastric cancer between January 1996 and December 2014 from the Fujian Medical University union hospital. Two trained research assistants collected and updated the database. And an attending doctor in our center reviewed it to ensure the authenticity of the record. The staging of the tumor was determined based on the eighth edition of the UICC TNM staging system in 2016 [14]. The study was approved by IRB of our institute (2017KY033).

2.2. Treatment methods

The inclusion criteria were as follows: (1) Definite pathological diagnosis of gastric malignant tumor before operation; (2) Without tumor invading the surrounding pancreas, spleen, liver and other organs (cT4b), or liver, lung, abdominal cavity, enlarged lymph nodes around the abdominal aorta and other distant metastasis (M1) by applying chest X-ray, abdominal ultrasound and abdominal CT/MRI examination; and (3) Patients who underwent D1 + or D2 lymph node dissection and with a pathological diagnosis of R0 resection. The exclusion criteria were as follows: (1) Intraoperative abdominal dissemination or distant metastasis; and (2) Patients with incomplete pathological diagnosis data. According to the second and third edition of the Gastric cancer treatment guidelines in Japan, the range of gastrectomy was selected and the lymph nodes around the stomach were removed [15,16]. Adjuvant chemotherapy was recommended for patients with advanced gastric cancer (pStage II and III). After 2007, neoadjuvant chemotherapy was recommended for patients with advanced gastric cancer [2]. 5-fluorouracil-based (5-Fu) chemotherapy such as cisplatin/oxaliplatin ± leucovorin plus capecitabine/S-1 were used, and six to eight cycles' adjuvant chemotherapy were recommended to the patients who meet the indications according to the NCCN Guidelines for gastric cancer [17–19].

2.3. SORT-related definitions

In this study, the previously reported Surgical Outcome Risk Tool (SORT) scoring system was applied for evaluation [8]. The formula was as follows:

SORT = (ASA − PS III × 1.411) + (ASA − PS IV × 2.388) + (ASA − PS V × 4.081) + (urgency 'expedited' × 1.236) + (urgency 'urgent' × 1.657) + (urgency 'immediate' × 2.452) + (high-risk specialty × 0.712) + (severity 'Xmajor complex' × 0.381) + (cancer × 0.667) + (age 65–79 years × 0.777) + (age ≥ 80 years × 1.591)

ASA − PS is short for American society of anesthesiologist physical status. The presence of these factors was defined as 1, with no risk factor of 0 (this study was performed on radical gastrectomy, so that high-risk surgical specialty, severity 'Xmajor complex' procedure and cancer were all recorded as 1), and the final result was the SORT score.

2.4. Prognosis and follow-up

In this study, outpatient, door visit, mail and telephone were used during follow-up. The follow-up interval was 3–6 months, and the patients were followed until the death of the patient or until Sep. 2016. The overall survival time was defined as the time interval from which the patient was operated on to any cause of death.

2.5. Statistical analysis

Continuous variables were expressed as mean ± SD and were tested by ANOVA. Categorical variables were examined by a $\chi 2$ test or a Fisher's exact test. The survival curve was drawn according to the Kaplan-Meier method, and the curve difference was checked by the log-rank method. Single factor and multiple factors of the independent prognostic factors were analyzed by COX regression. Variables with $p < 0.10$ in the univariate analysis were involved in the multivariate analysis [20]. Decision curve analysis (DCA) was used to report the clinical net benefit of using a SORT to select chemotherapy cases compared to treat-all and treat-none strategies. Graphically, the DCA is expressed as a curve, with benefit score on the vertical axis and probability thresholds on the horizontal axis. A curve is drawn for each approach that might be taken to establish a decision. Another line is drawn to show what happens when no treatment is ever given (black, Fig. 4), and another curve is drawn as if all patients receive treatment (gray). For any given patient's probability threshold, the curve with the highest benefit score at that threshold is the best choice [21]. When the p value was less than 0.05, the result was considered statistically significant. All the data were processed by the SPSS 18 statistical software package.

3. Results

3.1. SORT

A total of 5327 patients who underwent radical resection for gastric cancer between January 1996 and December 2014 were included in this study (Supplement figure 1). There were 767 cases with complications in the whole group, the incidence rate was 14.4%, 26 cases died within 30 days, and the mortality rate was 0.5%. The median SORT score for all the patients was 1.697 (IQR 1.697–2.474). In this study, 95% of the patients had SORT scores ranging from 1.69 to 3.30, and, to make it easy for clinical, a low-risk group was predefined as having SORT points < 2, the moderate group had 2 ≤ SORT < 3, and the high-risk group had a SORT ≥ 3.The complication rate in the low-risk group was 10.9%, and the mortality rate was 0.3%. The complication rate and the mortality rate were 18.4% and 0.5% in the moderate-risk group, respectively. Furthermore, in the high-risk group, the complication rate was 25.2% and the mortality rate was 1.5%. The incidence of complications and mortality in patients with gastric cancer is shown in Supplement figure 2.

The clinical and pathological data of the patients with gastric cancer are shown in Table 1. Compared with the moderate-risk group and the low-risk group, the patients were older ($p < 0.001$) in the high-risk group, were associated with a higher proportion of male patients ($p < 0.001$), had an ASA ≥ 3 ($p < 0.001$) and underwent an expedited surgery ($p < 0.001$).

3.2. Relationship between the SORT and prognosis

The median follow-up period for patients alive was 38 months. And there were 227 cases of patients were lost to follow up. Fig. 1 displays the survival of the patients with different SORT scores. The 5-year overall survival rate was 61.6%, 54.7% and 44.4% in the low-risk group (SORT < 2), the moderate-risk group (2 ≤ SORT < 3) and the high-risk group (SORT ≥ 3), respectively, and the difference was statistically significant (log-rank, $p < 0.001$). Further analysis of gastric cancer patients according to tumor staging revealed that the 5-year overall survival rate of the high-risk group was lower in the stage I-III patients than in the moderate- and low-risk group, and this was significantly different (log-rank, $p < 0.05$). Table 2 is an analysis of the factors affecting the overall survival of cancer patients after radical gastrectomy. Corresponding results showed that SORT, pTNM staging and postoperative complications were independent risk factors of gastric cancer prognosis, and postoperative chemotherapy was a protective factor for the prognosis of gastric cancer.

3.3. Chemotherapy benefit of a SORT

Fig. 2 illustrates the benefits of chemotherapy for patients with low-, moderate- and high-risk based on a SORT for those with advanced tumors (stage II and III) who required chemotherapy. A significant chemotherapy benefit was achieved for the stage II-III patients with a SORT < 2 and 2 ≤ SORT < 3 and for stage IIII patients with a SORT ≥ 3 ($p < 0.05$). However, chemotherapy did not improve the 5-year overall survival in the stage II patients with a SORT ≥ 3 (62.4% vs. 48.3%,$p = 0.196$). For patients with stage II and III gastric cancer, the adjusted OR value of postoperative chemotherapy is displayed in Supplement figure 3. The results indicated that a chemotherapy benefit was not found in the stage II patients with a SORT ≥ 3 only (OR = 0.639, 95% CI: 0.309–1.318, $p = 0.218$), and the rest of the subgroups received significant benefit from chemotherapy (OR < 1, $p < 0.05$).

3.4. Nomogram of chemotherapy

To provide a quantitative predictive approach for clinical workers to determine long-term survival differences after adjuvant chemotherapy, 2 nomogram models targeting chemotherapy and non-chemotherapy were established in the study by integrating SORT and other clinicopathological variables (Fig. 3). The difference between the two nomograms calculated in terms of whether or not to select postoperative adjuvant chemotherapy was the potential survival benefit of the patients who underwent chemotherapy. The C-index of the nomograms for chemotherapy and non-chemotherapy were 0.662 and 0.733, respectively.

3.5. Decision curve of chemotherapy

As shown in Fig. 4 of the established decision curve of chemotherapy, the results revealed that when the decision threshold of chemotherapy reached 20–52%, the patient achieved the greatest benefit, namely, the application of the above nomogram model to judge

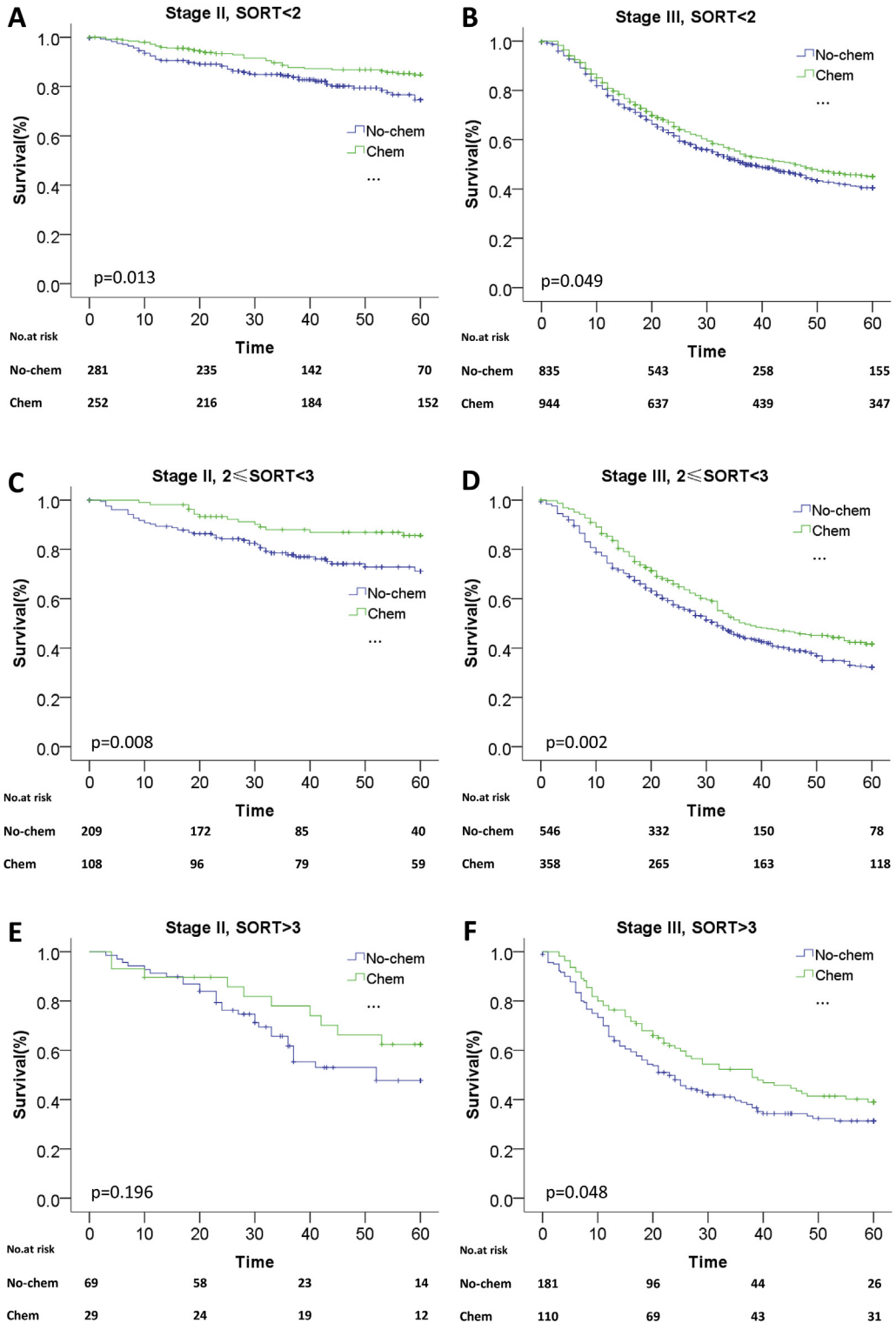

Fig. 2. Kaplan-Meier curves of patients with and without chemotherapy in pStage II and pStage III. (A) Stage II patients with SORT < 2, (B) Stage II patients with 2 ≤ SORT < 3, (C) Stage II patients with SORT ≥ 3, (D) Stage III patients with SORT points < 2, (E) Stage III patients with 2 ≤ SORT < 3, (F) Stage III patients with SORT ≥ 3.

whether chemotherapy or no chemotherapy, after the operation of gastric cancer, was more effective than the performance of chemotherapy or no chemotherapy uniformly in this group of patients. Moreover, the benefit of the nomogram model over chemotherapy decisions was superior to that of TNM staging or a SORT alone.

4. Discussion

The SORT scoring system is a useful tool proposed in the research published by Protopapa et al., and in their study, data from 326 hospitals were collected based on the outcome and death survey of the National Bureau of Secrets survey [8]. The final analysis showed that 6 preoperative readily available factors objectively and effectively

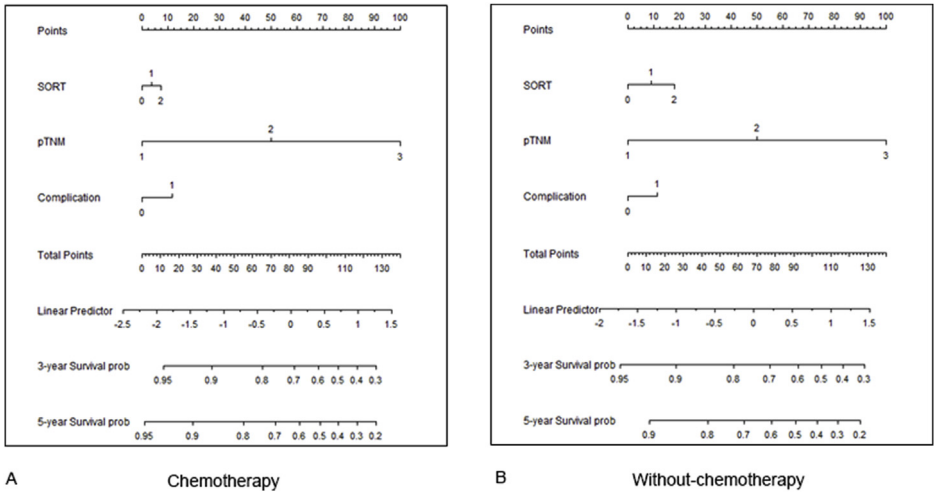

Fig. 3. Nomogram for overall survival in patients with gastric cancer. (A) Chemotherapy, (B) Without-chemotherapy. SORT = 0–2 represent low, moderate and high risk, respectively.

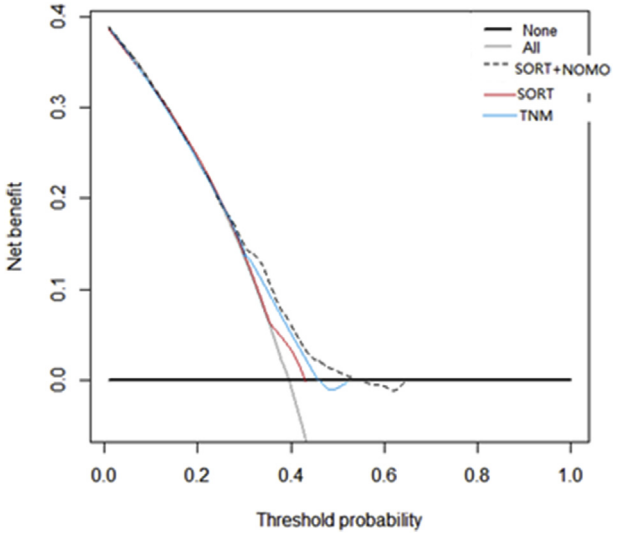

Fig. 4. Decision curve of chemotherapy.

quantified the risk factors for preoperative survival. In the validation group, the predictive accuracy of a SORT for postoperative short-term mortality was higher than that of the commonly used risk assessment tools, such as ASA-PS and SRS (a class of surgical severity). A SORT reflects the preoperative risk factors, which can be used to predict the short-term mortality after surgery and is closely related to long-term prognosis [8,13]. This study found that for patients with radical gastrectomy, a SORT was a simple and effective summary of the risk factors for patients with cancer beyond the TNM stage and was an independent prognostic factor for patients with gastric cancer. In clinical work, with respect to the question of whether physically poor patients should receive chemotherapy, this study also gave a reasonable quantitative tool and supported that adjuvant chemotherapy should be carefully applied for stage II patients with a SORT ≥ 3.

In the prior literature, scholars report the relationship between preoperative risk factors and long-term prognosis. Suzuki et al. discovered that the Charlson comorbidity index was an independent risk factor for squamous cell carcinoma of the respiratory tract [22]. In the study conducted by Solomon et al., in combination with comorbidity and functional status in elderly patients, a comprehensive geriatric assessment (CGA) evaluation system was designed to identify unresolved geriatric problems and to recommend interventions to improve functional status and long-term survival [23]. Furthermore, Chou et al. reported that in 20,632 patients with solid tumor resection, a SORT not only predicted mortality 1 year after the operation but also showed significant differences in the survival rates at 80 months after surgery in the patients with a different SORT [13]. In the present study, the prognosis of patients with a higher SORT was worse, which might be correlated with the fact that patients with a high SORT were not only susceptible to non-tumor associated comorbidities but also had a relatively low response to tumor cell proliferation and a lower level of immunity, resulting in decreased tumor-specific survival rates. In addition, Goldfarb et al. have shown that enhancing perioperative cellular immunity, as well as inhibiting excessive catecholamine and prostaglandin responses, effectively reduced immune suppression and the recurrence and metastasis of tumors [24]. Therefore, with an in-depth study of the prognosis of gastric cancer and the need for individualized survival prediction, the prognostic value of a SORT should be widely recognized and validated by the growing number of central data.

Since most RCT studies exclude patients with advanced age, comorbidities, and poor functioning, there is insufficient evidence as to whether postoperative adjuvant chemotherapy can be used in these populations, and it is difficult to guide clinical decision-making. This study reviewed and analyzed the stage II-III gastric cancer patients recommended for postoperative adjuvant chemotherapy according to the NCCN guidelines. It was found that there was no significant chemotherapy benefit on the 5-year overall survival rate in stage II patients with a SORT ≥ 3. A potential reason for this might be that stage II gastric cancer patients with a SORT ≥ 3 often have high-risk factors, such as advanced age, preoperative complications and poor functional status. The toxic and side effects of chemotherapy are obvious, and the benefit of chemotherapy is not significant accordingly. By contrast, in stage III gastric cancer patients with a SORT ≥ 3, although there are also high-risk factors leading to toxicity and side effects of chemotherapy, the prognosis of cancer is more pronounced due to the more advanced tumor, and the advantages of chemotherapy overweight the disadvantages. Furthermore, in this study, an independent prognostic risk factor for gastric cancer was used to construct a nomogram predictive model for predicting the benefit of chemotherapy. The difference in the nomograms was the extent of the patient's chemotherapy benefit. Quantification of the advantages and disadvantages of chemotherapy would be beneficial to clinical decision making. In addition, the decision curve further verified the application value of the nomogram. In fact, as a simple mathematical model, a decision curve can be used to evaluate the merits of statistical inference by introducing the loss function, which is widely used in evaluating the availability and

Table 1
Clinicopathological characteristics of patients undergoing radical gastrectomy.

	SORT			p
	< 2	2≤& < 3	≥3	
Age ± SD	53.35 ± 8.45	68.64 ± 6.80	71.19 ± 9.93	< 0.001
Gender				0.003
Male	2364	1288	376	
Female	886	321	92	
Charlson Index				< 0.001
0–2	3246	1589	417	
≥3	4	20	51	
ASA classification				< 0.001
1	2424	853	69	
2	826	756	131	
3	0	0	256	
4	0	0	12	
Neoadjuvant chemotherapy				0.024
No	3191	1585	452	
Yes	59	24	16	
Tumor diameter ± SD	50.88 ± 28.20	52.33 ± 27.62	54.07 ± 27.64	0.032
pT stage				< 0.001
T1	649	279	56	
T2	361	173	54	
T3	559	350	120	
T4a	1233	631	193	
T4b	448	176	45	
pN stage				0.333
N0	1043	501	131	
N1	436	242	67	
N2	559	294	92	
N3a	721	354	114	
N3b	491	218	64	
TNM stage				< 0.001
I	802	352	77	
II	563	319	99	
III	1885	938	292	
Gastrectomy				< 0.001
Open	1766	741	212	
Laparoscopic	1484	868	256	
Urgency of surgery				< 0.001
Elective	3250	1434	355	
Expedited	0	175	113	
Extent of resection				0.182
Total	1729	945	271	
Distal	1441	626	182	
Proximate	80	38	15	
Operative time ± SD	225.12 ± 73.89	216.05 ± 70.62	215.33 ± 70.32	< 0.001
Blood loss ± SD	155.80 ± 313.10	147.10 ± 205.00	144.54 ± 184.03	0.503
Adjuvant chemotherapy				< 0.001
No	1856	1057	313	
Yes	1394	552	155	

effectiveness of predictive models [25]. The results of this study documented that, according to the model, the clinician could achieve a better therapeutic benefit compared with the TNM stage alone or the application of postoperative chemotherapy or no postoperative chemotherapy in this group of patients. These results might provide an evidence-based incentive for chemotherapy in patients with poor physical condition. Nevertheless, due to the limitations of the chemotherapy data, this study is unable to solve whether the use of 5-FU monotherapy or reducing the dose of chemotherapeutic agents improves their long-term prognosis in this population.

In conclusion, A SORT is an independent risk factor for predicting the prognosis of gastric cancer, and postoperative adjuvant chemotherapy should be carefully adopted in stage II patients with a SORT≥3. The predictive models based on SORT and other

Table 2
Univariate and Multivariate Analyses for Overall Survival in patients after curative resection of gastric cancer.

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
All cases				
pStage II (vs I)	3.064(2.356–3.985)	< 0.001	3.120(2.398–4.060)	< 0.001
pStage III (vs I)	10.924(8.727–13.675)	< 0.001	11.290(9.007–14.151)	< 0.001
SORT≥3 (vs < 3)	1.553(1.338–1.803)	< 0.001	1.409(1.212–1.637)	< 0.001
Postoperation complication (vs. no)	1.485(1.321–1.669)	< 0.001	1.371(1.217–1.543)	< 0.001
Postoperation chemotherapy (vs. no)	1.084(0.990–1.187)	0.080	0.847(0.772–0.929)	< 0.001

clinicopathological variables can predict the benefit of chemotherapy quantitatively.

Conflicts of interest

There are no financial disclosures from any authors.

Funding

The study was sponsored by the National Key Clinical Specialty Discipline Construction program of China (No.[2012]649); the Key Projects of Science and Technology Plan of Fujian Province (No. 2014Y0025)and the Fund of Fujian Province science and technology innovation talents.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.11.008.

References

[1] H.H. Hartgrink, E.P. Jansen, N.C. van Grieken, C.J. van de Velde, Gastric cancer, Lancet 374 (2009) 477–490.
[2] D. Cunningham, W.H. Allum, S.P. Stenning, J.N. Thompson, C.J. Van de Velde, M. Nicolson, et al., Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, N. Engl. J. Med. 355 (2006) 11–20.
[3] M. Degiuli, M. Sasako, A. Ponti, A. Vendrame, M. Tomatis, C. Mazza, et al., Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer, Br. J. Surg. 101 (2014) 23–31.
[4] J.S. Macdonald, S.R. Smalley, J. Benedetti, S.A. Hundahl, N.C. Estes, G.N. Stemmermann, et al., Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction, N. Engl. J. Med. 345 (2001) 725–730.
[5] Y.J. Bang, Y.W. Kim, H.K. Yang, H.C. Chung, Y.K. Park, K.H. Lee, et al., CLASSIC trial investigators. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomized controlled trial, Lancet 379 (2012) 315–321.
[6] J. Lee, D.H. Lim, S. Kim, S.H. Park, J.O. Park, Y.S. Park, et al., Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial, J. Clin. Oncol. 30 (2012) 268–273.
[7] J. Lu, et al., The effectiveness of the 8th American Joint Committee on Cancer TNM classification in the prognosis evaluation of gastric cancer patients: a comparative study between the 7th and 8th editions, Eur. J. Surg. Oncol. 43 (12) (2017) 2349–2356.
[8] K.L. Protopapa, J.C. Simpson, N.C. Smith, et al., Development and validation of the surgical outcome risk tool (SORT), Br. J. Surg. 101 (13) (2014 Dec) 1774–1783.
[9] M. Saklad, Grading of patients for surgical procedures, Anesthesiology 24 (1941) 281–284.
[10] R. Sutton, S. Bann, M. Brooks, S. Sarin, The Surgical Risk Scale as an improved tool for risk-adjusted analysis in comparative surgical audit, Br. J. Surg. 89 (2002) 763–768.
[11] K.D. Zafirellis, A. Fountoulakis, K. Dolan, et al., Evaluation of POSSUM in patients with oesophageal cancer undergoing resection, Br. J. Surg. 89 (9) (2002 Sep) 1150–1155.
[12] S.R. Moonesinghe, M.G. Mythen, P. Das, K.M. Rowan, M.P.W. Grocott, Risk stratification tools for predicting morbidity and mortality in adult patients undergoing major surgery: qualitative systematic review, Anesthesiology 119 (2013) 959–981.
[13] W.C. Chou, F. Wang, Y.F. Cheng, et al., A simple risk stratification model that predicts 1-year postoperative mortality rate in patients with solid-organ cancer, Cancer Med 4 (11) (2015 Nov) 1687–1696.
[14] J.A. Ajani, H. In, T. Sano, M.B. Amin (Ed.), AJCC Cancer Staging Manual. 8, Springer-Verlag, New York, 2016.
[15] T. Nakajima, Gastric cancer treatment guidelines in Japan, Gastric Cancer 5 (1) (2002) 1–5.
[16] Japanese Gastric Cancer Association, Japanese gastric cancer treatment guidelines 2010 (ver. 3), Gastric Cancer 14 (2011) 113–123.
[17] S.H. Noh, S.R. Park, H.K. Yang, et al., Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial, Lancet Oncol. 15 (2014) 1389–1396.
[18] W. Koizumi, H. Narahara, T. Hara, et al., Randomized phase III study of S-1 alone versus S-1 + cisplatin in the treatment for advanced gastric cancer (The SPIRITS trial) SPIRITS: S-1 plus cisplatin vs S-1 in RCT in the treatment for stomach cancer, Lancet Oncol. 9 (2008) 215–221.
[19] J.A. Ajani, T.A. D'Amico, K. Almhanna, et al., Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Canc. Netw. 14 (10) (2016) 1286–1312.
[20] A.M. Almoudaris, R. Mamidanna, A. Bottle, P. Aylin, C. Vincent, O. Faiz, et al., Failure to rescue patients after reintervention in gastroesophageal cancer surgery in England, JAMA Surg. 148 (3) (2013) 272–276.
[21] A.J. Vickers, E.B. Elkin, Decision curve analysis, Med. Decis. Making 26 (6) (2006) 565–574.
[22] R. Suzuki, T. Kikutani, M. Yoshida, et al., The Charlson comorbidity index is a prognostic factor in sinonasal tract squamous cell carcinoma, Jpn. J. Clin. Oncol. 46 (7) (2016 Jul) 646–651.
[23] D.H. Solomon, Geriatric assessment: methods for clinical decision making, J. Am. Med. Assoc. 259 (16) (1988 Apr 22-29) 2450–2452.
[24] Y. Goldfarb, L. Sorski, M. Benish, B. Levi, R. Melamed, S. Ben-Eliyahu, Improving postoperative immune status and resistance to cancer metastasis: a combined perioperative approach of immunostimulation and prevention of excessive surgical stress responses, Ann. Surg. 253 (2011) 798–810.
[25] R.B. Den, K. Yousefi, E.J. Trabulsi, et al., Genomic classifier identifies men with adverse pathology after radical prostatectomy who benefit from adjuvant radiation therapy, J. Clin. Oncol. 33 (8) (2015 Mar 10) 944–951.