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ORIGINAL ARTICLE

Rates of Serious Complications Estimated by the ACS-NSQIP Surgical Risk Calculator in Predicting Oncologic Outcomes of Patients Treated with Pancreaticoduodenectomy for Pancreatic Head Cancer

Munseok Choi[1] · Chang Moo Kang[1,2] · Jae Uk Chong[3] · Ho Kyoung Hwang[1,2] · Dong Sup Yoon[1,2] · Woo Jung Lee[1,2]

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Abstract

Background The purpose of this study was to validate the predictive value of the oncologic outcome in addition to the validation of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) surgical risk calculator in patients treated with pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD) for pancreatic head cancer.

Methods From June 2005 to December 2014, 199 patients underwent PD or PPPD for pancreatic head cancer. Medical records were retrospectively reviewed for investigating general patient characteristics and any comorbid diseases. The calculated perioperative complication risks from the ACS NSQIP calculator were compared with observed complication rates. In a propensity score matching analysis, disease-free survival (DFS) and overall survival (OS) were estimated according to calculated severe complication rate (CSCR).

Results The CSCR > 17.9% ($n = 69$) and CSCR < 17.9% ($n = 130$) groups were significantly different considering number of the retrieved lymph nodes (22.95 ± 14.0 vs 18.80 ± 10.1, $p = 0.029$), histologic grade ($p = 0.0235$), and incidence of lymphovascular invasion ($p = 0.026$). The CSCR < 17.9% group had longer DFS (17.0 vs. 11.0 months, $p = 0.015$), but the OS was similar between the groups (39.0 vs. 23.0 months, $p = 0.48$). In the 1:2 propensity score analysis, the CSCR < 17.9% group had longer DFS and OS (DFS 26.0 vs. 11.0 months, $p = 0.009$; OS 44.0 vs. 26.0 months, $p = 0.023$).

Conclusion The ACS NSQIP surgical risk calculator predicts surgical risk in patients with pancreatic head cancer who undergo PD or PPPD. Furthermore, this tool can help predict the prognosis of surgically treated pancreatic head cancer.

Keywords Pancreaticoduodenectomy · Pancreatic head cancer · ACS NSQIP surgical risk calculator · Oncologic outcome

Introduction

Surgical resection remains the only potentially curative treatment of pancreatic cancer. Resection with clear microscopic margins is the only curative treatment for pancreatic cancer.[1–3] Early accounts of pancreaticoduodenectomy (PD) reported a mortality rate greater than 30%.[4] Improvements in operative techniques and postoperative care have caused mortality rates to drop to < 5% in the USA.[5,6] Despite significant reduction in mortality, however, morbidity remains common, occurring after 30% to 50% of procedures.[7]

Studies have reported on the potential impact of surgical complications associated with the oncologic outcomes of resected pancreatic cancer.[8–12] It is clear that preoperative risk factors are correlated with surgical complications after resection of pancreatic cancer.[13,14] For this reason, it is necessary to consider the preoperative risk factor before determining surgical resection in pancreatic cancer.

Recently, large-scale national databases have been used to assess various risk factors for perioperative mortality and

✉ Chang Moo Kang
cmkang@yuhs.ac

[1] Division of Hepatobiliary and Pancreatic Surgery, Yonsei University College of Medicine, Ludlow Faculty Research Building #203, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea

[2] Pancreaticobiliary Cancer Clinic, Yonsei Cancer Center, Severance Hospital, Seoul, South Korea

[3] Department of Surgery, National Health Insurance Service Ilsan Hospital, Goyang, South Korea

morbidity. This has facilitated the development of mortality risk tools, such as the American College of Surgeons National Surgical Quality Improvement Program's (ACS NSQIP) surgical risk calculator that has been widely adopted as a decision aid and informed consent tool by surgeons and patients. Preoperative and postoperative data from more than 2.7 million records, with operation dates between 2010 and 2014, from 586 ACS NSQIP participating hospitals are available. It can be used in a web-based tool that calculates the risk of 11 post-operative complications within 30 days of surgery.[15,16]

There are several studies to validate the predicting capacity of ACS NSQIP surgical risk calculator in pancreatic surgery. Specifically, Balzano et al. found that the preoperative score was proven to be reliable in forecasting 1-year mortality in patients with resectable pancreatic cancer.[17] However, to date, no studies have tested the potential usefulness of the ACS NSQIP surgical risk calculator even to predict the long-term oncologic outcomes in patients with resected pancreatic head cancer. Therefore, this study was performed (1) to validate the ACS NSQIP surgical risk calculator in its ability to predict surgical complication and (2) to test the potential feasibility of the ACS NSQIP surgical risk calculator to predict long-term oncologic outcomes of patients with resected pancreatic head cancer by their calculated serious complication rate (CSCR).

Materials and Methods

Patients and Data Collection

This study was approved by the Institutional Review Board of Yonsei University College of Medicine. From January 2005 to December 2014, the medical records of 199 patients were retrospectively reviewed, who underwent PD or PPPD for pancreatic head cancer. In our group, there were five surgeons over the 9-year period who performed a PD or PPPD for pancreatic head cancer. Three surgeons performed most of the resections.

Estimation and Validation of the ACS NSQIP Surgical Risk Calculator

Nineteen preoperative variables, as defined within the calculator, were reviewed and entered for individual patients within the dataset. Estimated risks of postoperative outcomes were then calculated using the ACS NSQIP surgical risk calculator's website (http://www.riskcalculator.fac.org/) and the predicted risks of the 11 postoperative complications (serious complication, any complication, pneumonia, cardiac complication, surgical site infection (SSI), urinary tract infection (UTI), venous thromboembolism (VTE), renal failure, readmission, return to the OR, death) as well as predicted length of hospital stay and rates of discharged to nursing or rehab facility were recorded. ACS NSQIP has supplied precise definitions and exact thresholds for postoperative outcomes.[18]

The performance of the surgical risk calculator was evaluated using the Brier score (BS). The BS measures the accuracy of probabilistic predictions. It is defined as the average squared difference between patients' predicted probabilities and observed outcomes, which were defined as either 1 or 0 that corresponds to an event or nonevent. The BS approaching 0 indicates perfect prediction.

Cut-off Values for Calculated Serious Complication Rate to Predict Oncologic Outcomes

To find out whether the ACS NSQIP surgical risk calculator can function as a predictive model of survival as well as mortality and morbidity, we yielded a cut-off value through the relationship between the calculated serious complication rate (CSCR) and disease-free survival (DFS). The cut-off value was determined using the Contal and O'Quigley method, which calculates the maximizing hazard ratio (HR) based on log rank statistics and estimates the best cut-off value, 17.9%.[19]

Propensity Score Matching Analysis

Propensity score matching was adopted to reduce the bias from several confounding variables. A propensity score was generated by binary logistic regression, and then patients with similar propensity scores were selected from the dataset (1:2 matching). Univariate and survival analysis were performed in the propensity-matched population as well as the total population.

Other Statistical Analysis

All statistical analyses were performed with SPSS Statistical software (version 23.0, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviations or ranges, and categorical variables were expressed as frequencies or percentages. Student's t tests were used for comparing continuous variables, and chi-squared tests and Fisher's exact tests were used for comparing categorical data. The Kaplan–Meier method was applied for analysis of DFS and OS. A Cox proportional hazards analysis was performed to estimate prognostic factor for disease-specific OS in propensity-matched population. A p value < 0.05 was considered to be statistically significant.

Results

Patient Characteristics

A total of 199 patients with pancreatic head cancer who had undergone PD or PPPD were enrolled in this study. PPPD was predominantly utilized ($N = 179$, 81.9%). Eighty patients were female and 119 were male, with a mean age of 61.5 years (range 37–83 years). Most of the patients were < 65 years (54.4%), had ASA class II–III disease (88.3%), and had an independent functional status (100%, Table 1).

Table 1 Patients characteristics of resected pancreatic head cancer

Characteristics	*N* (%)
Age group	
< 65 years	111 (54.4)
65–74 years	80 (39.2)
75–84 years	13 (37)
> 85 years	0
Sex	
Female	80 (40.2)
Male	119 (59.8)
Functional status	
Independent	199 (100)
Partially dependent	0
Totally dependent	0
ASA class	
Healthy patient	19 (9.5)
Mild systemic disease	116 (58.2)
Severe systemic disease	60 (30.1)
Severe systemic disease that is a constant threat to life	4 (2.2)
Diabetes	
None	111 (55.7)
Oral	65 (32.6)
Insulin	23 (11.7)
Hypertension	80 (40.2)
CHF within 30 days	0
Dyspnea	
None	191 (96.0)
At rest	8 (4.0)
Moderate exertion	0
Smoker	51 (25.6)
History of severe COPD	0
Dialysis	1 (0.5)
Acute renal failure	0
Chronic steroids	1 (0.5)
Ascites within 30 days	6 (2.9)
Emergency case	0

Validation of ACS NSQIP Calculator

Of 199 patients who underwent resection for pancreatic head cancer, the serious complication rate, any complication rate, and SSI rate were higher (16.6%, 29.6%, and 17.1%, respectively). The rate for other complications was less than 2%. Within the entire cohorts, the BS for serious complications, any complication, and SSI were higher (0.149, 0.215, and 0.154, respectively). However, the BS for patients in the entire cohort was generally lower than those of the null model, reflecting good prediction of the risk calculator (Table 2).

Long-Term Oncologic Outcomes in Patients with Resected Pancreatic Head Cancer According to CSCR, 17.9%

In the overall comparative analysis, patients within the CSCS < 17.9% group showed more favorable pathological characteristics, such as the number of the retrieved lymph nodes ($p = 0.029$), lower histologic grade ($p = 0.0235$), and a lower incidence of lymphovascular invasion ($p = 0.026$). Other clinicopathological characteristics were not significantly different between the two groups (Table 3). Subsequently, on survival analysis for the total population, the DFS was 17 months (95% CI 0.00–38.545) in the CSCR < 17.9% group and 11 months (95% CI 9.281–12.719) in the CSCR > 17.9% group, which was statistically significant (p value = 0.015, Fig. 1A). However, there were no significant differences in the OS between the CSCR < 17.9% group and CSCR > 17.9% group

Table 2 Correlation between calculated risk and outcomes for the ACS NSQIP surgical risk calculator

Outcomes	*N* (observed)	%	Brier score	Brier score (null model)
Serious complication	36	16.67	0.149	0.176
Any complication	64	29.63	0.215	0.319
Pneumonia	2	0.93	0.010	0.010
Cardiac complication	1	0.46	0.005	0.005
SSI[a]	37	17.13	0.154	0.186
UTI[b]	0	0.00	0.002	0.000
VTE[c]	3	1.39	0.014	0.015
Renal failure	0	0.00	0.000	0.000
Return to OR[d]	0	0.00	0.018	0.000
Death	1	0.46	0.011	0.010
Discharge to NH[e] or rehabilitation	2	0.93	0.005	0.005

[a] Surgical site infection
[b] Urinary tract infection
[c] Venous thromboembolism
[d] Operation room
[e] Nursing home

Table 3 Comparison of clinicopathologic features between CSCR ≤ 17.9% group and CSCR > 17.9% group

	Total population			Propensity-matched population		
	Calculated serious complication rate		*p* value	Calculated serious complication rate		*p* value
	≤ 17.9% (*n* = 69)	> 17.9% (*n* = 130)		≤ 17.9% (*n* = 50)	> 17.9% (*n* = 100)	
Neoadjuvant CCRT			0.6462			0.8000
No	26 (35.6)	49 (38.8)		14 (9.3)	30 (20.0)	
Yes	47 (64.3)	77 (61.1)		36 (24.0)	70 (46.7)	
Tumor size (cm)	2.13 ± 0.9	2.37 ± 1.2	0.1218	2.28 ± 0.8	2.32 ± 1.1	0.791
T stage			0.2760			0.657
T0	4 (5.4)	4 (3.1)		0 (0.0)	1 (0.7)	
T1	3 (4.1)	9 (7.1)		2 (1.3)	7 (4.7)	
T2	1 (1.3)	0 (0)		1 (0.7)	0 (0.0)	
T3	64 (87.6)	113 (89.6)		46 (30.7)	92 (61.3)	
T4	1 (1.3)	0 (0)		1 (0.7)	0 (0.0)	
N stage			0.1499			0.488
N0	39 (53.4)	54 (42.8)		26 (17.3)	46 (30.7)	
N1	34 (46.5)	72 (57.1)		24 (16.0)	54 (36.0)	
Retrieved LN	22.95 ± 14.0	18.80 ± 10.1	0.0290	20.94 ± 9.3	18.67 ± 9.9	0.181
Histologic grade			0.0235			0.477
Well	16 (24.6)	13 (11.2)		10 (6.7)	14 (9.3)	
Moderate	13 (64.6)	95 (81.9)		35 (23.3)	79 (52.7)	
Poor	6 (9.2)	8 (6.9)		5 (3..3)	7 (4.7)	
Undifferentiated	1 (1.5)	0 (0)		0 (0.0)	0 (0.0)	
PNI			0.1794			0.480
No	28 (38.89)	36 (29.51)		17 (11.4)	29 (19.5)	
Yes	44 (61.11)	86 (70.49)		32 (21.5)	71 (47.7)	
LVI			0.026			0.265
No	53 (27.5)	80 (41.5)		37 (24.7)	65 (43.3)	
Yes	14 (7.3)	46 (23.8)		13 (8.7)	35 (23.3)	
R status			0.9206			0.514
R0	62 (84.93)	109 (86.51)		44 (29.3)	83 (55.3)	
R1	10 (13.70)	16 (12.7)		5 (3.3)	16 (10.7)	
R2	1 (1.37)	1 (0.79)		1 (0.7)	1 (0.7)	
Completion of chemotherapy			0.057			0.785
Well	37 (26.8)	68 (49.3)		27 (25.5)	51 (48.1)	
Dose reduction	5 (3.6)	16 (11.6)		5 (4.7)	13 (12.3)	
Drop	5 (3.6)	7 (5.1)		4 (3.8)	6 (5.7)	
Adjuvant chemotherapy			0.5769			0.800
No	23 (31.51)	35 (27.78)		14 (9.3)	30 (20.0)	
Yes	50 (68.49)	91 (72.22)		36 (24.0)	70 (46.7)	
Period to chemotherapy (days)	52.72 ± 19.93	58.96 ± 23.74	0.1172	54.77 ± 20.7	58.37 ± 23.7	0.444
Hospital stay (days)	38.29 ± 86.78	36.28 ± 67.37	0.8650	41 ± 104.4	30 ± 15.5	0.304

PNI perineural invasion, *LVI* lymphovascular invasion

(39 months [95% CI 19.127–58.873] vs. 23 months [95% CI 15.764–30.236], $p = 0.48$, Fig. 2A).

In the 1:2 propensity score-matched analysis, previous statistical differences disappeared in terms of number of retrieved lymph nodes ($p = 0.187$), histologic grade ($p = 0.447$), and lymphovascular invasion ($p = 0.487$, Table 3). However, it was found that the CSCR < 17.9% group still showed better DFS than the CSCR > 17.9% group (26 months [95% CI 0.000–52.134 vs. 11 months [95% CI 9.326–12.674], $p = 0.009$, Fig. 1B). Moreover, the CSCR < 17.9% group showed

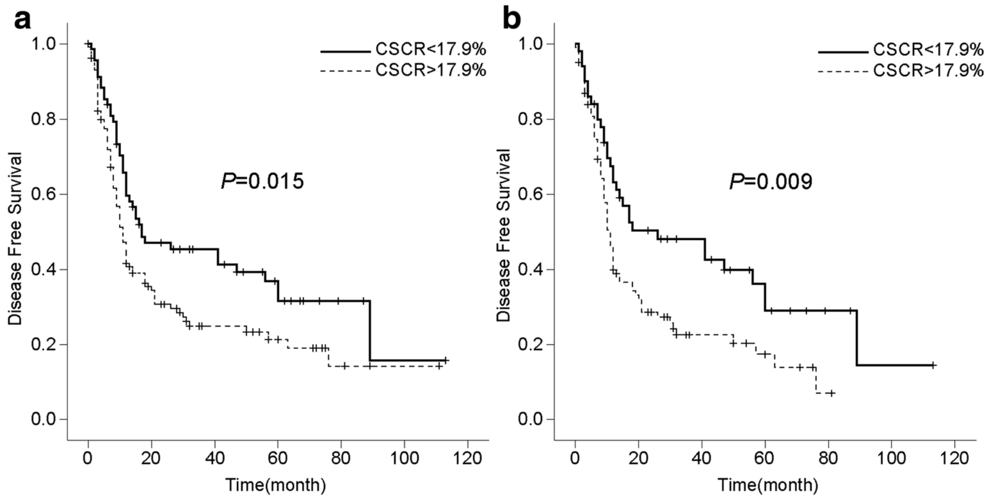

Fig. 1 **A** Kaplan-Meier survival curves representing disease-free survival for pancreaticoduodenectomy (n = 199) in total population. **B** Kaplan-Meier survival curves representing disease-free survival for pancreaticoduodenectomy (n = 150) after propensity score-matched analysis

better OS than the CSCR > 17.9% group (44 months [95% CI 25.389–62.611] vs. 26 months [95% CI 17.011–34.989], p value = 0.023, Fig. 2B).

In addition, there was no statistical difference in terms of the length of hospital stay (p = 0.304), and even the time period to starting postoperative chemotherapy (p = 0.304) in the 1:2 propensity score-matched analysis. However, patients with a higher CSCR tended to receive delayed postoperative chemotherapy (rho = 0.168, p = 0.0467, Fig. 3).

Discussion

In managing pancreatic cancer, margin-negative resection of pancreatic cancers has proven to be the most effective treatment to date. In addition, postoperative adjuvant chemotherapy should be mandatory for completing cancer treatment. Postoperative complications are associated with delayed recovery, delayed postoperative adjuvant chemotherapy, or even with omission of chemotherapy.[10,12] Merkow et al.[10] assessed the impact of postoperative complications on the receipt of postoperative adjuvant chemotherapy. They found that 23.2% had at least 1 serious complication among 2017 patients who underwent resection for stage I–III pancreatic cancer. Serious complications not only increased the likelihood of not receiving adjuvant chemotherapy over twofold (odds ratio = 2.20, 95% CI 3.59–16.87) but also doubled the likelihood of delaying adjuvant treatment administration (odds ratio = 2.08, 95% CI 1.42–2.54). Recently, Watanabe et al.[11] investigated the impact of postoperative complications on survival after curative resection for pancreatic cancer. Thirty-one percent of patients suffered a major postoperative complication. In a multivariate analysis, no postoperative major complications were identified as independent favorable factors for recurrence-free survival (hazard ratio = 0.48, 95% CI 0.28–0.85) and OS (hazard ratio = 0.47, 95% CI 0.27–0.81). We also have reported detrimental effects of postoperative complications on oncologic efficacy of R0 pancreatectomy in ductal adenocarcinoma of the pancreas.[9] Therefore, preoperatively identifying patients at increased risk for postoperative

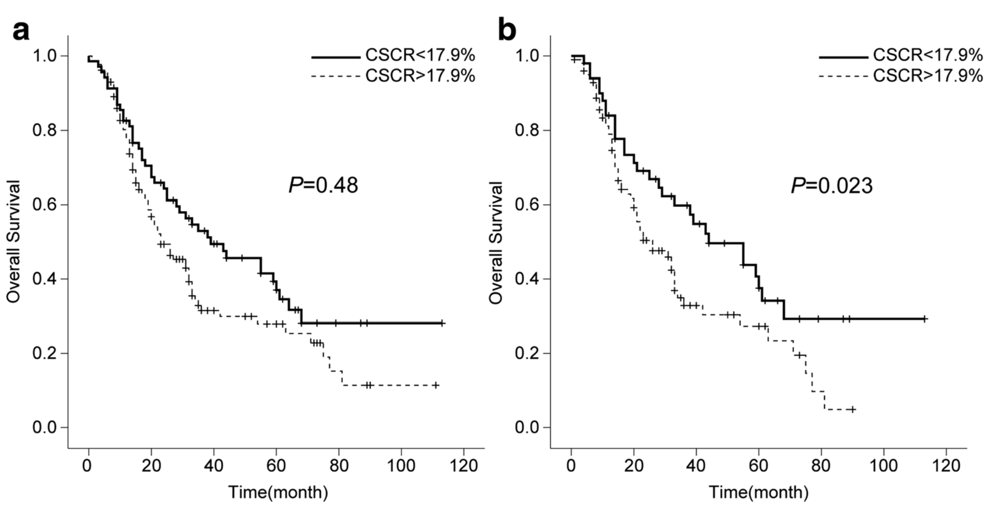

Fig. 2 **A** Kaplan-Meier survival curves representing overall survival for (n = 199) in total population. **B** Kaplan-Meier survival curves representing overall survival for pancreaticoduodenectomy (n = 150) after propensity score-matched analysis

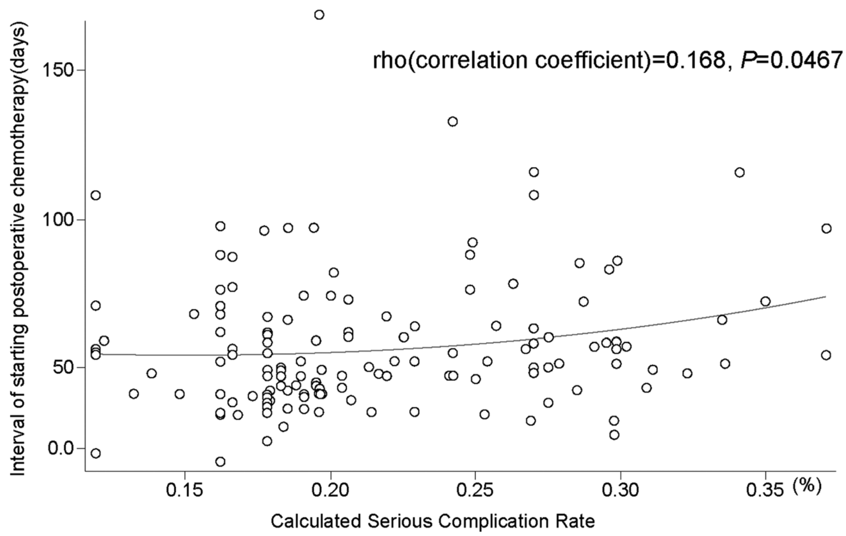

Fig. 3 Although there is no statistical significance, it confirms the tendency between high CSCR and length of hospital stay

severe complications is thought to be very important in predicting oncologic outcomes. Understanding potential risk of perioperative complications and survival outcome should be crucial to provide informed consent, and it can influence decision making in choosing treatment options.

In 2013, the ACS-NSQIP risk calculator was introduced to utilize the predicted perioperative risk in clinical practice. Several other studies in recent years have examined utility of the ACS NSQIP risk calculator in specific elective patient populations and specific surgical technique including oncology, colorectal, reconstructive, lumbar, gynecologic, and acute care surgery.[20] In spite of some controversy,[21] it has been found that the ACS NSQIP risk calculator is an effective tool for estimating the rate of expected postoperative complications in an individual surgical patient. In addition, it will be useful as a tool to determine the need for surgical treatment by providing information on postoperative complications and mortality to patients and caregivers. Specifically, it will be important for dealing with patients who plan to have a complex surgical procedure, such as PD in pancreatic cancer, which can carry a significant risk of postoperative complications, as well as poor survival outcome even after surgery.

The utility and validation of the ACS NSQIP calculator have been studied in PD patients with pancreatic cancer. Greenblatt et al. used the NSQIP database including 4945 patients with PD to determine preoperative risk factors for serious complications and mortality after PD. They concluded that preoperative factors are associated with perioperative outcomes after PD,[5] and the prediction tool can estimate the probability of early morbidity and mortality in patients undergoing PD. McMillan et al. demonstrated that the current ACS NSQIP surgical risk calculator does not adequately predict mortality risk after PD; however, the incorporation of procedure specific risk greatly improves its accuracy.[22] Gianpaolo et al. also reported a model for predicting early death after surgery using a simple risk score calculated in association with preoperative factors in pancreatic cancer patients.[17]

When considering pancreatic cancer surgery, surgeons need to think over not only potential perioperative complications but also potential survival benefit for the patients. Therefore, it would be worthy if surgeons and patients could get additional information to predict even long-term oncologic outcome through the ACS NSQIP surgical risk calculator, as well as postoperative procedure-related risk. To our knowledge, this is the first study to test the potential application of the ACS NSQIP surgical risk calculator in resected pancreatic head cancer patients to predict long-term oncologic outcome, as well as clinical validation of predicting power for postoperative complications. In this study, it is interesting to note that the ACS NSQIP risk calculator can predict not only the morbidity and mortality of 30 days post-operative, but also long-term oncologic outcomes such as DFS and OS. This observation was more discriminated in propensity score matching analysis. According to our results, the cut-off value for the calculated serious complication rate (CSCR) was determined to be 17.9%. It is thought that the exact cut-off point may need to be further investigated using a much larger study population; however, our current study suggests that even long-term oncologic outcomes of resected pancreatic cancer could be predicted based on a serious complication rate calculated by ACS NSQIP risk calculator.

Why is it that increased CSCR can predict oncologic outcome in resected pancreatic head cancer? Until now, no concrete mechanisms have been proven. We previously have proposed that postoperative complications,[9] intraoperative transfusions,[23] and postoperative pain[24] can be important prognostic factors in patients with resected pancreatic cancer. These clinical circumstances are not related to the tumor biology, and therefore, it is suggested that prognosis of patients with resected pancreatic cancer can be influenced not only by biologic behavior of the pancreatic cancer itself but also by host factors of pancreatic cancer patients. This hypothesis is supported by our propensity score analysis. There were no statistical differences in terms with short-term oncologic outcomes according to CSCR; however, it was found that high CSCR clearly demonstrated unfavorable long-term survival outcomes in resected pancreatic head cancer.

The clinical variables required for ACS NSQIP surgical risk calculator seem to represent the reflection of general condition of the patients like a Charlson comorbidity index (CCI)[25] and cumulative illness rating scale (CIRS).[26] Recently, Kos et al.[27] evaluated the effect of comorbidity calculated by CCI and CIRS on survival of pancreatic cancer. They demonstrated that the median OS rate was 9.4 (95% CI 6.7–12.1) months in the patients with CCI scores ≤ 2 and 6.2 (95% CI 4.0–8.3) months in those with CCI scores ≥ 3 with statistical significance ($p = 0.05$). Asano et al.[28] also suggested that the Charlson age comorbidity index (CACI) could predict prognosis in patients with resected pancreatic cancer, because patients who received chemotherapy showed significantly lower CACI (87.0% vs. 69.0%, $P < 0.001$), subsequently, the OS rate was significantly higher in the low CACI group than in the high CACI group ($p = 0.047$). On the other hand, as shown in other studies, the present observation that higher CSCR was related to delayed chemotherapy might be one of the causes that influence oncologic outcome in resected pancreatic head cancer. However, Mirkin et al.[29] retrospectively reviewed the national cancer data base (2003–2011) and concluded that the earlier initiation of adjuvant chemotherapy did not influence on long-term survival in patients with resected pancreatic cancer. The exact underlying mechanisms remain to be investigated further in the near future.

There are several inherent limitations of this study. First, it is a single-center retrospective study; therefore, our results may not be consistent with the results of other centers. In addition, we have to admit that the contents and the severity of complication were based on medical record, which could be a significant selection bias in interpreting data when correlating oncologic outcomes. Second, our study is based on a small sample size, contributing to the low event rates and precludes specific conclusions about the predictive accuracy of the calculator. Therefore, future multi-center prospective studies are needed to validate this study.

In conclusion, the ACS-NSQIP surgical risk calculator predicts the perioperative surgical risk in patients with resected pancreatic head cancer. In addition, the calculated severe complication rate could be used as a predictive factor for the prognosis of surgically treated pancreatic head cancer. Based on the present results, a patient-oriented surgical approach needs to be emphasized even in “resectable” patients with pancreatic cancer. The present observation may show the rationale for selective application of neoadjuvant chemotherapy in resectable pancreatic cancer, such as in those with a calculated high severe complication rate. From that point of view, Katz et al.[30] already proposed the concept of neoadjuvant chemotherapy or chemoradiation therapy followed by pancreatectomy in patients with marginal performance status. More large volume data are needed to validate the current potential relationships between high CSCR and unfavorable long-term oncologic outcome in resected pancreatic cancer.

Author Contributions Munseok Choi acquired and analyzed the data and drafted the manuscript. Jae Uk Chong and Ho Kyoung Hwang acquired and analyzed the data and revised the manuscript. Dong Sup Yoon and Woo Jung Lee revised the manuscript. Chang Moo Kang conceived and designed the study, revised, and gave final approval to the manuscript.

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