Original Article

Creatinine-to-cystatin C ratio as a marker of skeletal muscle mass for predicting postoperative complications in patients undergoing gastric cancer surgery

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Background: Gastric cancer patients usually suffer from skeletal muscle depletion. The serum creatinine/cystatin C ratio (CCR) is a new, simple tool that could serve as a biomarker of skeletal muscle mass. This study explored the ability of the preoperative CCR to predict postoperative complications in patients with gastric cancer.

Methods: A total of 309 patients with gastric cancer who were undergoing surgery were enrolled in this study. Univariate analyses were conducted to determine the potential risk factors for postoperative complications, and multivariate analyses were used to determine the independent influencing factors of postoperative complications. A receiver operating characteristic curve was conducted to identify the optimal cutoff value of the CCR. Patients were divided into two groups according to the critical value to investigate the relationship between the CCR and postoperative complications.

Results: Postoperative complications occurred in 87 patients. Multivariate analysis suggested that age, red blood cell level, lymphocyte count, cystatin C, CCR, and N factor were independent risk or protective factors for postoperative complications (P<0.001). The optimal cutoff value of the preoperative CCR was 7.117. Compared with the high preoperative CCR group, patients with a low preoperative CCR were more likely to have both mild complications (P<0.001) and major complications (P<0.001).

Conclusions: The preoperative CCR can effectively predict postoperative complications in gastric cancer patients after surgery.

Keywords: Serum creatinine/cystatin C (Scr/CysC); skeletal muscle depletion; gastric cancer; postoperative complications

Submitted Nov 28, 2020. Accepted for publication Mar 12, 2021.

doi: 10.21037/apm-20-2366

View this article at: http://dx.doi.org/10.21037/apm-20-2366

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Introduction

Sarcopenia is a syndrome characterized by a reduction in skeletal muscle mass and function (1). Recently, increasing evidence has shown that sarcopenia assessed by a third lumbar (L3) computed tomography (CT) slice can be a prognostic predictor in digestive tract cancer and inflammatory bowel disease (IBD) (1,2). Skeletal muscle depletion is the major characteristic of sarcopenia, and many studies have also demonstrated that skeletal muscle depletion is associated with poor outcomes after surgery (1,2). According to the mechanisms of sarcopenia in various diseases, muscle protein synthesis is affected by inflammatory cytokines, such as interleukin-6 (3).

Many studies have confirmed that skeletal muscle mass is independently associated with postoperative complications in gastric cancer patients. Therefore, numerous studies suggest early screening of skeletal muscle mass in patients with gastric cancer, and supportive nutritional treatment should be given to those patients with skeletal muscle depletion (4-6). The traditional detection methods used to measure skeletal muscle mass, such as CT scans, are costly and complex. Hence, the application of these methods is limited. Therefore, it is necessary to identify other indicators that are more intuitive, less expensive and more reliable for predicting skeletal muscle mass (7).

Serum creatinine (Scr) and cystatin C (CysC) are usually employed to estimate renal function in clinical practice (8). Scr is a metabolic waste product produced by creatine in skeletal muscle. However, fluid resuscitation and augmented renal clearance can affect Scr levels (9). Furthermore, CysC can be produced by all nucleated cells in the body at a constant production rate and only removed by glomerular filtration. CysC is used as an endogenous marker to reflect changes in the glomerular filtration rate and is uninfluenced by inflammatory processes, sex, age, or nutritional status (10,11). Some studies have supported that the Scr/CysC ratio (CCR) may serve as a biomarker of skeletal muscle mass. These results indicate that the CCR is a simple and inexpensive measure that can be used to evaluate the skeletal muscle mass of patients with malignancies, such as gastric cancer (12-16). However, whether this ratio can be regarded as a predictive marker of postoperative complications in gastric cancer patients has not been reported.

Therefore, the purpose of the present study was to investigate whether the CCR can be used as an index to predict postoperative complications in gastric cancer patients and to determine the cutoff value of the CCR for further evaluation. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2366).

Methods

Patients

The clinical records of gastric cancer patients who underwent surgery at Sir Run Run Shaw Hospital from June 2016 to June 2019 were collected and retrospectively analyzed. The inclusion criteria were as follows: (I) gastric cancer was diagnosed by endoscopy and pathology results, (II) patients underwent curative gastrectomy, (III) no other tumor was found before the operation, and (IV) patients were between 18 and 75 years old. The exclusion criteria were as follows: (I) unavailability of preoperative CCR within one week, (II) emergency or urgent surgery, (III) history of renal insufficiency [calculated creatinine clearance <30 mL/min or urinary albumin (ALB) >300 mg/d] (17), (IV) palliative surgery for gastric cancer, or (V) combination with other tumors or pregnancy. The present study met the requirements of and was approved by the Ethics Committee of Sir Run Run Shaw Hospital (No. 20170616). This study was conducted in according with the Declaration of Helsinki (as revised in 2013). The Human Research Committee of Sir Run Run Shaw Hospital waived the need for informed consent.

Data collection

Patients' baseline characteristics and preoperative laboratory data (ALB, Scr, CysC, hemoglobin (Hb), red blood cell (RBC), and preoperative C-reactive protein (CRP) levels), intraoperative data, and postoperative outcomes within 30 days after surgery or before hospital discharge were collected. The cancer stage was recorded according to the eighth edition of the American Joint Committee on Cancer (AJCC) (1).

Postoperative complications

Postoperative complications appearing within 30 days after surgery or before hospital discharge were recorded according to the Clavien-Dindo classification (18). Mild complications were defined as Clavien-Dindo grade I or II, while major complications were defined as Clavien-Dindo grades III–IV. The postoperative hospital stay was

also recorded. Surgical site infection (SSI) included surface incisional infection and deep space infection (19).

Statistical analysis

Statistical analysis was carried out by using SPSS 21.0 software (Armonk, NY, USA: IBM Corp). Continuous variables are presented as the mean ± standard deviation (SD). Categorical variables are presented as numbers (percentages). Normally distributed data were analyzed using Student's *t*-test, while Pearson's chi-square test was used to analyze categorical variables. According to the incidence of postoperative complications, a receiver operating characteristic (ROC) curve was constructed to determine the optimal critical value. Univariate analyses were performed to determine the potential independent risk factors for postoperative complications. The potential independent risk factors determined by univariate analyses were included in the logistic regression for multivariate analysis. A difference with P<0.05 was considered to be statistically significant.

Results

Baseline characteristics of patients

In total, 380 patients with gastric cancer underwent gastrectomy during the study period, and 71 patients were excluded from the study. The baseline characteristics of the patients are shown in *Table 1*. Finally, 309 gastric cancer patients undergoing surgery were enrolled in this study, including 228 (73.8%) males and 81 (26.2%) females. A total of 87 (28.2%) patients had postoperative complications after gastrectomy.

Potential independent risk factors for postoperative complications according to the univariate analyses

The patients were divided into a postoperative complication group and a non-postoperative complication group. The baseline characteristics, intraoperative data and preoperative laboratory data for each group are shown in *Table 1*. Preoperative concurrent diseases, BMI, tumor markers, operation time and estimated blood loss all showed no significant differences between the two groups. However, there were significant differences between groups for age, preoperative serum Hb levels, preoperative CRP level, preoperative RBC level, preoperative ALB level, preoperative lymphocyte count, preoperative CysC level, CCR, pathological stage (T1, T4, N0 and N3) and TNM stage (stage I and stage III). Patients in the non-postoperative complication group had lower preoperative CRP levels and higher preoperative serum Hb, RBC, ALB, and lymphocyte levels (3.5±0.6 *vs.* 9.3±1.9, P<0.001; 127.9±1.4 *vs.* 113.8±3.0, P<0.001; 4.28±0.04 *vs.* 3.78±0.08, P<0.001; 40.0±0.3 *vs.* 36.4±0.6, P<0.001; 1.65±0.04 *vs.* 1.34±0.06, P<0.001, respectively) than patients in the postoperative complication group. Notably, patients in the non-postoperative complication group had significantly lower preoperative serum CysC levels than patients in the postoperative complication group (0.92±0.01 *vs.* 1.05±0.03, respectively, P<0.001), while the CCR was significantly higher in patients in the non-postoperative complication group (9.41±0.14 *vs.* 8.35±0.23, P<0.001).

Analysis of independent risk factors for postoperative complications by multivariate analysis

The results of the multivariate analysis showed that age [odds ratio (OR): 2.383, 95% confidence interval (CI): 1.227–4.625, P=0.010], preoperative CysC level (OR: 2.146, 95% CI: 1.101–4.180, P=0.025) and a pathological stage of N3 (OR: 2.288, 95% CI: 1.026–5.103, P=0.043) were all independent risk factors for postoperative complications in gastric cancer patients. In contrast, the preoperative lymphocyte count (OR: 0.359, 95% CI: 0.145–0.889, P=0.027), preoperative RBC level (OR: 0.139, 95% CI: 0.048–0.399, P<0.001) and CCR (OR: 0.315, 95% CI: 0.137–0.723, P=0.006) were independent protective factors against postoperative complications in gastric cancer patients, as shown in *Table 2*.

ROC curve of the CCR (for predicting postoperative complications)

Multivariate analysis confirmed that the CCR was associated with postoperative complications. To determine the optimal critical value of the CCR, ROC curves based on postoperative complications were plotted. The area under the curve was 0.625, the sensitivity was 0.908 and the specificity was 0.286. The positive predictive value was 56.5%, and the negative predictive value was 75.3%. The highest Youden index was 0.194, and the corresponding optimal cutoff value of the CCR was identified as 7.117, as shown in *Figure 1*.

Table 1 Study population and baseline characteristics depended on with or without postoperative complications

Characteristics	Non-postoperative complications (n=222)	Postoperative complications (n=87)	P value
Age, y	61.5±0.7	68.2±1.1	<0.001
Gender (male/female)	162/60	66/21	0.604
BMI, kg/m^2	22.9±0.2	22.3±0.3	0.115
Comorbidities			
Diabetes mellitus	24 (10.8)	14 (16.1)	0.204
Hypertension	78 (35.1)	39 (44.8)	0.114
History of abdomen surgery	50 (22.5)	20 (23.0)	0.930
Hb, g/L	127.9±1.4	113.8±3.0	<0.001
CRP, mg/L	3.5±0.6	9.3±1.9	<0.001
WBC, 10^9/L	5.9±0.1	5.9±0.2	0.981
RBC, 10^{12}/L	4.28±0.04	3.78±0.08	<0.001
Platelet, 10^9/L	217.2±4.4	216.0±7.8	0.886
Albumin, g/L	40.0±0.3	36.4±0.6	<0.001
Lymphocyte, 10^9/L	1.65±0.04	1.34±0.06	<0.001
Scr, mg/dL	0.84±0.01	0.84±0.02	0.831
CysC, mg/L	0.92±0.01	1.05±0.03	<0.001
Scr/CysC ratio	9.41±0.14	8.35±0.23	<0.001
CA-125, μ/mL	12.8±1.0	15.5±1.4	0.143
CA-199, μ/mL	23.0±3.1	40.2±14.1	0.091
CEA, ng/mL	6.0±2.3	5.1±1.0	0.799
AFP, μg/L	3.3±0.3	3.2±0.3	0.896
Types of operative procedure			0.098
Distal gastrectomy	145 (65.3)	48 (55.2)	–
Total gastrectomy	77 (34.7)	39 (44.8)	–
Intraoperative fluid utilization, mL	2,189±41	2,090±69	0.2118
Operation time, min	271.5±3.7	272.8±5.5	0.837
Estimated blood loss, mL	99.2±8.9	123.6±12.3	0.135
T factor			
T1	78 (35.1)	13 (14.9)	<0.001
T2	27 (12.2)	8 (9.2)	0.459
T3	26 (11.7)	16 (18.4)	0.123
T4	91 (41.0)	50 (57.5)	0.009

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Non-postoperative complications (n=222)	Postoperative complications (n=87)	P value
N factor			
N0	95 (42.8)	23 (26.4)	0.008
N1	30 (13.5)	14 (16.1)	0.560
N2	43 (19.4)	10 (11.5)	0.099
N3	54 (24.3)	40 (46.0)	<0.001
pTNM stage			
I	84 (37.8)	18 (20.7)	0.004
II	42 (18.9)	9 (10.3)	0.068
III	90 (40.5)	58 (66.7)	<0.001
IV	6 (2.7)	2 (2.3)	0.839

Values in parentheses are percentages unless indicated otherwise; the other values are mean ± SE. BMI, body mass index; Hb, hemoglobin; CRP, C-reactive protein; WBC, white blood cells; RBC, red blood cells; Scr, serum creatinine; CysC, cystatin C.

Table 2 Multivariate analysis of postoperative complications in gastric cancer patients undergoing surgery

Characteristics	Multivariate		
	OR	95% CI	P value
Age	2.383	1.227–4.625	0.010
Hb	0.424	0.168–1.073	0.070
CRP	1.058	0.382–2.930	0.914
RBC	0.139	0.048–0.399	<0.001
ALB	0.465	0.198–1.093	0.079
Lymphocyte	0.359	0.145–0.889	0.027
CysC	2.146	1.101–4.180	0.025
Scr/CysC ratio	0.315	0.137–0.723	0.006
T factor			
T1	0.853	0.253–2.877	0.798
T4	1.286	0.532–3.107	0.576
N factor			
N0	0.681	0.194–2.394	0.549
N3	2.288	1.026–5.103	0.043
pTNM stage			
I	0.421	0.101–1.762	0.236
III	2.975	0.885–10.005	0.078

Hb, hemoglobin; CRP, C-reactive protein; ALB, white blood cells; RBC, red blood cells; Scr, serum creatinine; CysC, cystatin C.

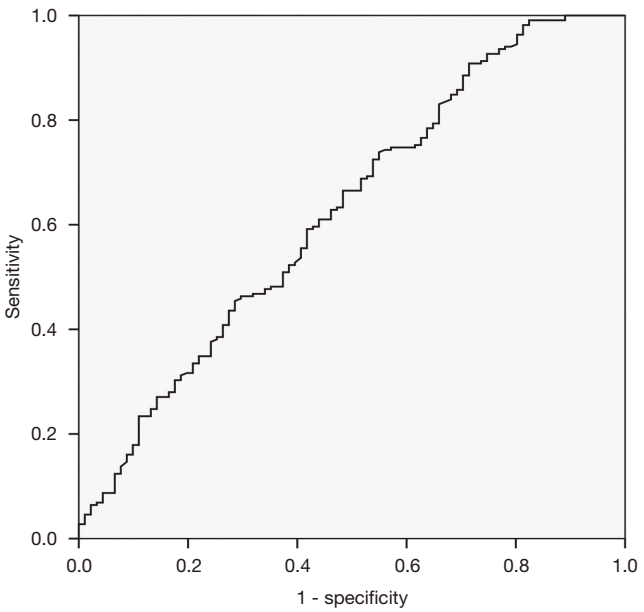

Figure 1 Receiver operating characteristic (ROC) curve showing creatinine-to-cystatin C ratio before surgery predict postoperative complications of gastric cancer.

Comparison of complications between the high and low CCR groups

According to the optimal critical value of the CCR, patients were divided into a low CCR group and a high CCR group

Table 3 Comparison of postoperative complications in gastric cancer undergoing surgery with low and high CCR

Characteristic	CCR <7.117 (n=46)	CCR ≥7.117 (n=263)	P value
Overall complications	25 (54.3)	62 (23.6)	<0.001
Mild complications (grade I to II)	20 (43.5)	36 (13.7)	<0.001
Fever >38.5 ℃ after surgery	4 (8.7)	4 (1.5)	0.017
Incision infection	1 (2.2)	2 (0.8)	0.421
TPN >2 weeks	7 (15.2)	5 (1.9)	<0.001
Postoperative blood transfusion	5 (10.9)	8 (3.0)	0.032
Gastroplegia	0 (0)	1 (0.4)	0.571
Early postoperative bowel obstruction	3 (6.5)	13 (4.9)	0.661
Chylous leakage	0 (0)	3 (1.1)	0.325
Major complications (grade III to grade IV)	27 (58.7)	44 (16.7)	<0.001
Postoperative hemorrhage	3 (6.5)	9 (3.4)	0.348
Ascites	3 (6.5)	7 (2.7)	0.215
Pleural effusion	2 (4.3)	1 (0.4)	0.041
intestinal obstruction	4 (8.7)	5 (1.9)	0.030
Intra-abdominal abscess	3 (6.5)	6 (2.3)	0.158
Anastomotic leakage	3 (6.5)	3 (1.1)	0.040
Anastomotic bleeding	2 (4.3)	2 (0.8)	0.095
Anastomotic stenosis	2 (4.3)	3 (1.1)	0.167
Duodenal stump fistula	2 (4.3)	3 (1.1)	0.167
Septic shock	0 (0)	1 (0.4)	0.571
Single organ dysfunction	3 (6.5)	4 (1.5)	0.070
Dead cases (grade V)	0 (0)	1 (0.4)	0.571
Surgical site infection	9 (19.6)	14 (5.3)	0.003
Surface incisional infection	1 (2.2)	2 (0.8)	0.421
Deep space infection	8 (17.4)	12 (4.6)	0.004
Postoperative stay	19.0±2.1	12.7±0.4	<0.001

Values in parentheses are percentages unless indicated otherwise; the other values are mean ± SE. CCR, serum creatinine/cystatin C ratio; TPN, total parenteral nutrition; SSI, surgical site infection.

(*Table 3*). Compared with the high CCR group, the low CCR group had a higher incidence rate of postoperative complications [25 (54.3%) *vs.* 62 (23.6%), P<0.001]. Specifically, the incidence of mild complications was 20 (43.5%) in the low CCR group and 36 (13.7%) in the high CCR group (P<0.001), including fever (temperature >38.5 ℃) after surgery [4 (8.7%) *vs.* 4 (1.5%), P=0.017], continuous total parenteral nutrition for more than 2 weeks [7 (15.2%) *vs.* 5 (1.9%), P<0.001] and postoperative blood transfusion [5 (10.9%) *vs.* 8 (3.0%), P=0.032]. The incidence of major complications was 27 (58.7%) in the low CCR group and 44 (16.7%) in the high CCR group (P<0.001), including postoperative intestinal obstruction [4 (8.7%) *vs.* 5 (1.9%), P=0.030], pleural effusion [2 (4.3%) *vs.* 1 (0.4%), P=0.041], and anastomotic leakage [3 (6.5%) *vs.* 3 (1.1%), P=0.040]. With regard to SSI, surface incisional infection

occurred in 3 (1.0%) cases, while deep space infection occurred in 20 (6.5%) cases in total. There seemed to be no correlation between the CCR and postoperative surface incisional infection. However, the incidence of deep space infection was significantly higher in the low CCR group [8 (17.4%) *vs.* 12 (4.6%), P=0.004]. The postoperative hospitalization stay in the low CCR group was significantly longer than that in the high CCR group (19.0±2.1 *vs.* 12.7±0.4, P<0.001).

Discussion

The relationship between preoperative CCR and postoperative complications was discussed in the present study. For gastric cancer patients undergoing surgery, the results revealed that the preoperative CCR was independently associated with postoperative complications, indicating that a low preoperative CCR is associated with a high risk of postoperative complications.

The skeletal muscle mass accounts for 40–50% of the human body (20). Skeletal muscle plays an important role in human metabolism and is the main storage site of proteins in the body (21). The loss of skeletal muscle mass is the main characteristic of sarcopenia. Sarcopenia and skeletal muscle depletion not only affect disease prognosis but also may impose a great burden on national medical expenditures (22).

Skeletal muscle depletion will reduce cardiopulmonary function, wound healing ability and activity ability, increase complications such as infection and deep vein thrombosis, prolong the postoperative hospital stay, slow the rehabilitation process and reduce quality of life (23,24). Skeletal muscle depletion assessed by CT has been reported as an independent risk factor for poor prognosis in cancers, such as gastric cancer (25-28). A study by Zhuang *et al.* hypothesized why skeletal muscle depletion assessed by CT scan can independently predict the postoperative prognosis in patients with gastric cancer (29). First, patients with skeletal muscle depletion have a lower BMI and hypoalbuminemia, and BMI and ALB have previously been associated with complications. Second, the loss of muscle mass and function will reduce physical activity and independent living abilities in daily life and hinder normal recovery after surgery. Third, the incidence of postoperative infection in patients with skeletal muscle depletion is much higher and the length of hospital stay is longer than that in patients with normal skeletal muscle mass (30,31). Thus, a preoperative assessment of skeletal muscle mass is very important for predicting postoperative complications and guiding early interventions.

Muscle catabolism can produce creatinine, and its production is directly proportional to muscle mass. Hence, the Scr level is considered to be a potential marker that can reflect systemic muscle mass. However, this marker is not useful in practice because renal function can influence its level. In contrast, CysC cannot be affected by systemic muscle mass because it is produced in all nucleated cells and has been reported to be another marker of glomerular filtration. Recently, because it has been reported as an index of sarcopenia, the CCR was suggested to be a new marker of skeletal muscle mass (16,32,33).

Compared with traditional detection methods, such as dual-energy X-ray absorptiometry, bioimpedance analysis and CT, detection of the CCR involves only blood sampling, which is convenient for analysis, and patients do not need to bear high detection costs, such as the costs of CT. Therefore, the CCR is more readily accepted. In addition, the CCR results are intuitive and easy to understand. Therefore, it is convenient for clinicians to use the CCR to evaluate skeletal muscle mass. The present study explored the role of the preoperative CCR in predicting the short-term prognosis of gastric cancer patients undergoing surgery, and the results showed a correlation between the preoperative CCR and short-term postoperative complications.

Data were collected and analyzed by univariate and multivariate analyses to explore the potential risk factors related to postoperative complications in gastric cancer patients. The results showed that the preoperative CCR was independently associated with postoperative complications. In addition, the study also indicated that age, preoperative lymphocyte count, preoperative CysC level and a TNM stage of N3 were independent risk factors for postoperative complications and that the preoperative RBC count was an independent protective factor against postoperative complications. In conclusion, advanced age, anemia and malnutrition play adverse roles in the postoperative prognosis of gastric cancer patients undergoing surgery.

Furthermore, to distinguish the risk of postoperative complications, we plotted a ROC curve. The optimal cutoff value of the CCR was 7.117 based on the ROC curve. The statistical analysis showed that gastric cancer patients with a low preoperative CCR are more likely to develop postoperative complications after surgery, including both

mild and severe complications. Patients with SSIs (34) usually have severe complications and infections involving drug-resistant bacteria, which can increase the difficulty of treatment. Our results found no significant difference in surface incisional infection, while the incidence of deep space infection was higher in the low CCR group. Patients with a low preoperative CCR also had longer postoperative hospitalization stays. Therefore, the CCR may serve as a simple and useful new diagnostic index for diagnosing sarcopenia and can predict the short-term prognosis of gastric cancer patients undergoing surgery.

However, our research also has some limitations. First, this is a single-center study. Second, selection bias may exist in this retrospective study. Finally, based on studies in the literature, the CCR can represent the skeletal muscle mass, but we did not use CT or other detection methods to verify the existence of sarcopenia in this study. Therefore, prospective multicenter studies are needed to confirm the predictive effect of the CCR for postoperative prognosis (35).

Conclusions

As a new, simple, easily measured and effective tool to evaluate skeletal muscle mass, the CCR can reliably predict postoperative complications in gastric cancer patients, which could help clinicians evaluate the precise preoperative risk stratification.

Acknowledgments

We are grateful to Huatong Liu from the Australian National University for her help with language editing.
Funding: This work was supported by the (National Natural Science Foundation of China) under Grant (number 81800474), (Guangxi University Young and Middle-aged teachers' basic scientific research ability improvement project) under Grant (number 2019ky1541), and (Zhejiang Provincial Natural Science Foundation) under Grant (number Q19H030064).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-2366

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-2366

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2366). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou, China (No. 20170616) and individual consent for this retrospective analysis was waived. This study was conducted in according with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Gao J, Liang H, Qian Y, Pan J, Liu W, Qi W, Zhou W, Ge X, Wang X. Creatinine-to-cystatin C ratio as a marker of skeletal muscle mass for predicting postoperative complications in patients undergoing gastric cancer surgery. Ann Palliat Med 2021;10(5):5017-5026. doi: 10.21037/apm-20-2366

