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The impact of preoperative ASA-physical status on postoperative complications and long-term survival outcomes in gastric cancer patients

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Abstract. – OBJECTIVE: The aim of this study was to investigate the impact of the preoperative American Society of Anesthesiologists-Physical status (ASA-PS) on both the short-term and long-term outcomes in patients with Gastric Cancer (GC).

PATIENTS AND METHODS: In a retrospective observational study, a total of 473 GC patients were divided into the following 3 groups: ASA 1, ASA 2, and ASA 3-4.

RESULTS: The ASA 3-4 group included significantly older patients compared to the other groups (*p*<0.0001). In ASA 1 patients, there was a higher number of lymph nodes dissected (*p*=0.006), and more patients received adjuvant treatment (*p*<0.001). In the three groups, no difference regarding the postoperative surgical and medical complications (*p*=0.29 and *p*=0.1, respectively) nor in terms of mortality rate (*p*=0.17) were demonstrated. The multivariate analysis showed that age, tumor stage, number of lymph nodes dissected, positive lymph nodes, adjuvant treatments, and postoperative surgical complications were significant predictive factors for mortality. Five-year overall and disease-free survival for ASA 1, ASA 2, and ASA 3-4 groups was 56%, 57.6%, and 44%, respectively; and 37%, 44.3%, and 39.2%, respectively.

CONCLUSIONS: Preoperative ASA-PS alone cannot serve as a direct operative risk indicator for GC patients.

Key Words:
Gastric cancer, ASA-Physical status, Morbidity, Mortality.

Introduction

The American Society of Anesthesiologists-Physical status (ASA-PS) classification system offers to clinicians a simple categorization of patients' physiological status, which can be helpful predicting surgical risks. ASA-PS classification system was first introduced in 1941[1] and includes nowadays, after continuous updates over the past years, 6 PS categories[2-4]. Categories 1-5 (6 denotes an organ donor) represent increasingly patient impairment scores: ASA 1 representing a normal healthy patient and ASA 5 a moribund patient who is not expected to survive without the operation[5]. Today, ASA class is recorded for any surgical case performed under anesthesia. ASA-PSis is significantly associated with postoperative morbidity and mortality[6-11]. However, important bias, such as single-institution datasets, patient variables, and sample size limits predictive power. It remains unclear if the ASA-PS can be considered an independent predictor of surgical and medical complication predictor in a large variety of surgical patients from different institutions. ASA-PS is not validated yet as an outcome predictor, and criticism has been raised regarding the subjectivity of the measure[12]. We evaluated the ASA-PS classification system as an independent risk stratification metric for short-term and long-term outcomes in GC patients.

Patients and Methods

We retrospectively reviewed all medical records (retrieved from our patient database) of all patients who underwent gastrectomy from January 2005 to December 2015 at the Digestive Surgery Department of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Italy. The institutional review board approval was prelim-

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inarily obtained, and the same surgical team performed all surgical procedures. A total of 473 preoperatively assessed GC patients were divided into the following 3 groups: ASA class 1, ASA class 2, and ASA class 3. Our ASA class 3 group only included additionally ASA class 4 patient for convenience. No patient was in the ASA group 5.

Clinicopathological Evaluation

The evaluated parameters included patient demographics, comorbidity, surgical procedure details, and postoperative complications. The tumor depth, nodal status, and disease stage were classified according to the 8th American Joint Committee on Cancer Staging System[13] and lymph node dissection, according to the Japanese Gastric Cancer Association Guidelines[14].

Short-Term Surgical Outcomes and Long-Term Survival Outcomes

Short-term surgical outcomes were based on perioperative surgical outcomes such as GC stage, neoadjuvant and adjuvant treatment, surgery type, harvested lymph node numbers, positive lymph nodes, postoperative surgical and medical complications, mortality, and recurrence rates. We considered all postoperative complications within 30 days from surgery defined as severity grade 2 or more according to the Clavien-Dindo classification[15]. The postoperative mortality was defined as death within 30 days from surgery. Patients received follow-up until their death, and the date of the last follow-up, recurrence-related information, disease-free survival (DFS), death-related information, and overall survival (OS) were obtained to determine the long-term survival outcomes. As far as combined treatments are concerned, the perioperative chemotherapy was administered according to the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) protocol[16]. The oncologists decided about adjuvant chemotherapy administration, as previously reported[17], resulting in heterogeneity regarding chemotherapy, treatment protocols, and a number of cycles performed.

Statistical Analyses

All variables are expressed as mean ± standard deviation (±). A 1-way variance analysis was used to evaluate continuous variables among the 3 groups and the χ^2 or Fisher's exact tests were used to evaluate the categorical variables. Multivariate logistic regression analyses were used to assess the factors associated with postoperative complications. DFS and OS were calculated from the date of the surgery. The survival adjusted for censoring was calculated using the Kaplan-Meier method, and the medians were compared using the log-rank test. Cox proportional hazards model was used to assess the multivariate prognostic factors. A p value <0.05 was considered statistically significant.

Results

During the study period, a total of 473 patients with GC underwent surgery with curative intent. Patients' demographics, surgical details, and pathologic characteristics are shown in Table I. ASA 3-4 group contained significantly older patients compared to the other groups (p<0.0001). In ASA 1 patients there was a higher number of lymph nodes dissected (p=0.006) and more patients received adjuvant treatments (p<0.001). In the three groups no difference in terms of postoperative surgical and medical complications (p=0.29 and p=0.1, respectively) and in terms of mortality rate (p=0.17) was noted. The mean length of the postoperative hospital stay for the three groups was 7.6 (±3.8), 9.2 (±3.6), and 10.2 (±5.1), respectively (p=0.32). The comparison of the clinicopathologic patient characteristics according to stratified ASA group in GC patients < 65 years (n=153) and > 65 years (n=320) are shown in Table II. Regarding patients ≤65 years old, only postoperative medical complications and perioperative mortality rate were statistically significant among the three groups. Among patients with age >65 years old, only the adjuvant treatments were statistically significant among the three groups. The median follow-up was 82 months (range, 8-157 months). The follow-up data were collected in 441 cases (93.2%), excluding 25 patients lost during the study period and 7 patients who died during the postoperative hospital stay. At the last evaluation, 282 (59.6%) patients died. Table III shows the results of the multivariate analysis of the prognostic factors effects on mortality. Age, tumor stage, number of lymph nodes dissected, positive lymph nodes, adjuvant treatments, and postoperative surgical complications were significant predictive factors for mortality. The five-year overall survival for ASA 1, ASA 2, and ASA 3-4 groups was 56%, 57.6%, and 44%, respectively (p=ns) (Figure 1). The five-year disease-free survival for ASA 1, ASA 2, and ASA 3-4 groups was 37%, 44.3%,

Table I. Comparison of clinicopathologic characteristics of patients according to stratified ASA score (n = 473).

	ASA 1 (n = 54)	ASA 2 (n = 311)	ASA 3-4 (n = 108)	p
Age, years (± SD)	44.7 (± 8.8)	64.5 (± 8.2)	77.5 (± 6.3)	< 0.0001
Gender, n (%)				0.74
Male	29 (53.7)	184 (59.2)	62 (57.4)	
Female	25 (46.3)	127 (40.8)	46 (42.6)	
Stage, n (%)				0.98
Early (I-II)	30 (55.5)	175 (56.3)	60 (55.5)	
Advanced (III-IV)	24 (44.5)	136 (43.7)	48 (44.5)	
Neoadjuvant treatment, n (%)	2 (3.7)	24 (7.7)	9 (8.3)	0.53
Type of surgery, n (%)				0.44
Distal gastrectomy	29 (53.7)	167 (53.7)	71 (65.7)	
Total gastrectomy	19 (35.2)	108 (34.7)	24 (22.2)	
Superior polar resection	5 (9.2)	18 (5.8)	7 (6.4)	
Total degastro-gastrectomy	1 (1.8)	18 (5.7)	6 (5.5)	
Number of lymph nodes, n (± SD)	31.4 (± 17.6)	29.3 (± 15.5)	24.4 (± 13.8)	0.006
Positive lymph nodes, n (± SD)	6.6 (± 9.6)	5.9 (± 8.8)	4.8 (± 7.2)	0.38
Adjuvant treatment, n (%)	36 (66.7)	157 (56.1)	16 (16.5)	< 0.0001
Post-operative surgical complications*, n (%)	3 (5.6)	40 (12.9)	12 (11.1)	0.29
Post-operative medical complications*, n (%)	4 (7.4)	59 (19)	21 (19.4)	0.1†
Mortality rate, n (%)	0 (0)	5 (1.6)	1 (0.9)	0.23
Length of stay, days (± SD)	7.6 (± 3.8)	9.2 (± 3.6)	10.2 (± 5.1)	0.32
Recurrence rate**, n (%)	14 (29.2)	68 (23.8)	21 (21.4)	0.58

* > Clavien-Dindo grade II. †chi-square test: - ASA 1 *vs*. ASA 2: $p = 0.049$ - ASA 1 *vs*. ASA 3-4: $p = 0.04$; **432 patients (41 lost at follow up).

Table II. Comparison of clinicopathologic characteristics of patients according to stratified ASA score in GC patients with age < 65 years (n=153) and > 65 years (n = 320).

Characteristics	Age ≤ 65 y (n = 153)			p	Age > 65 y (n = 320)			p
	ASA 1 (n = 50)	ASA 2 (n = 102)	ASA 3-4 (n = 1)		ASA 1 (n = 4)	ASA 2 (n = 209)	ASA 3-4 (n = 107)	
Gender, n (%)								0.36
Male	28 (56)	59 (57.8)	0	0.5	1 (25)	125 (59.8)	62 (57.9)	
Female	22 (44)	43 (42.2)	1 (100)		3 (75)	84 (40.2)	45 (42.1)	
Stage, n (%)								0.71
Early (I-II)	27 (54)	55 (53.9)	1 (100)	0.65	3 (75)	120 (57.4)	59 (55.1)	
Advanced (III-IV)	23 (46)	47 (46.1)	0		1 (25)	89 (42.6)	48 (44.9)	
Neoadjuvant treatment, n (%)	2 (4)	5 (4.9)	0	0.94	0	19 (9.1)	9 (8.4)	0.8
Type of surgery, n (%)				0.72				0.24
Distal gastrectomy	27 (54)	55 (53.9)	0		2 (50)	112 (53.6)	71 (66.4)	
Total gastrectomy	18 (36)	41 (40.2)	1 (100)		1 (25)	67 (32.1)	23 (21.5)	
Superior polar resection	4 (8)	5 (4.9)	0		1 (25)	13 (6.2)	7 (6.5)	
Total degastrectomy	1 (2)	1 (1)	0		0	17 (8.1)	6 (5.6)	
Number of lymph nodes, n (± SD)	32 (±18)	32 (±16.7)	49	0.62	23.2 (±8.9)	27.8 (± 14.7)	24 (± 13)	0.09
Positive lymph nodes, n (± SD)	7.1 (±9.8)	7.2 (±9.9)	0	0.76	0.5 (±1)	5.3 (8.2)	4.9 (7.2)	0.45
Adjuvant treatment, n (%)	35 (70)	66 (64.7)	0	0.30	1 (25)	91 (51.1)	16 (16.7)	< 0.0001
Post-operative surgical complications, n (%)	3 (6)	13 (12.7)	0	0.42	0	27 (12.9)	12 (11.2)	0.68
Post-operative medical complications, n (%)	4 (8)	15 (14.7)	1 (100)	0.018	0	44 (21.1)	20 (18.7)	0.53
Length of stay, days (± SD)	7.2 (± 4.3)	8.7 (± 3.9)	12 (± 0)	0.46	9.6 (± 4.7)	10.2 (± 3.5)	11.6 (± 6.9)	0.71
Mortality, n (%)	0	2 (1.9)	1 (100)	< 0.0001	0	3 (1.4)	0	0.77
Recurrence*, n (%)	13 (26)	20 (22.5)	0	0.77	1 (25)	48 (22.9)	21 (19.6)	0.41

*432 patients (41 lost at follow up).

Table III. Multivariate logistic regression for mortality.

Predictive factors	Mortality		
	Odds ratio	95% confidence interval	*p*
Age	1.5	1.01-2.24	0.04
Gender	0.97	0.66-1.44	0.91
ASA score	0.7	0.5-1.08	0.14
Stage	1.6	1.13-2.49	0.009
Neoadjuvant treatment	0.6	0.28-1.55	0.35
Type of surgery	1.12	0.86-1.47	0.37
Number of lymph nodes	1.03	1.01-1.05	< 0.0001
Positive lymph nodes	0.95	0.92-0.98	0.001
Adjuvant treatment	0.59	0.36-0.97	0.04
Post-operative surgical complications	2.8	1.37-5.94	0.005
Post-operative medical complications	0.89	0.48-1.62	0.7

and 39.2%, respectively (*p*= ns) (Figure 2). The statistical significance was only reached comparing the ASA 2 *vs.* ASA 3 groups 5-year overall survival (*p*=0.016).

Discussion

The surgical risk assessment can be complex, and several risk scores have been introduced over the past years. A globally used risk-score is the ASA-PS. We retrospectively investigated the preoperative ASA-PS score impact on the short-term surgical and long-term oncological outcomes of 473 GC patients undergoing surgery. Our work represents the only experience in the literature analyzing the impact of ASA-PS on short-term and long-term outcomes in patients with GC. As for other surgical procedures, also for GC ASA-PS revealed import-

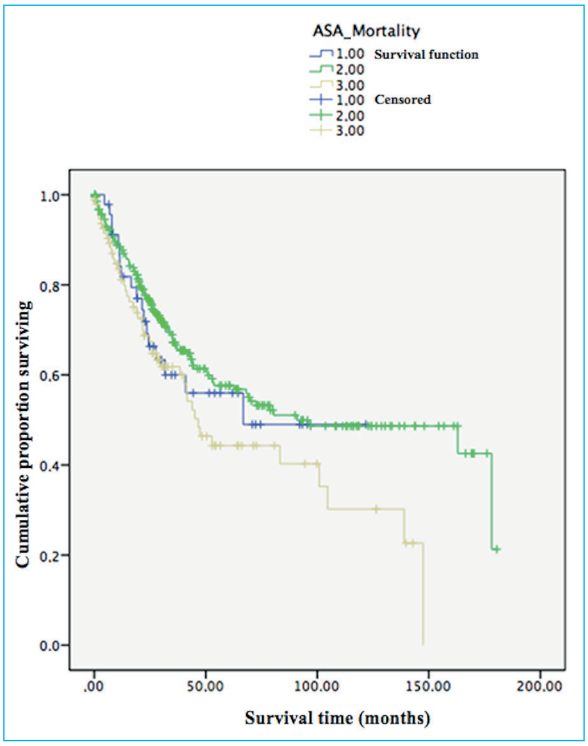

Figure 1. 5-year overall survival for all patients of the study group.

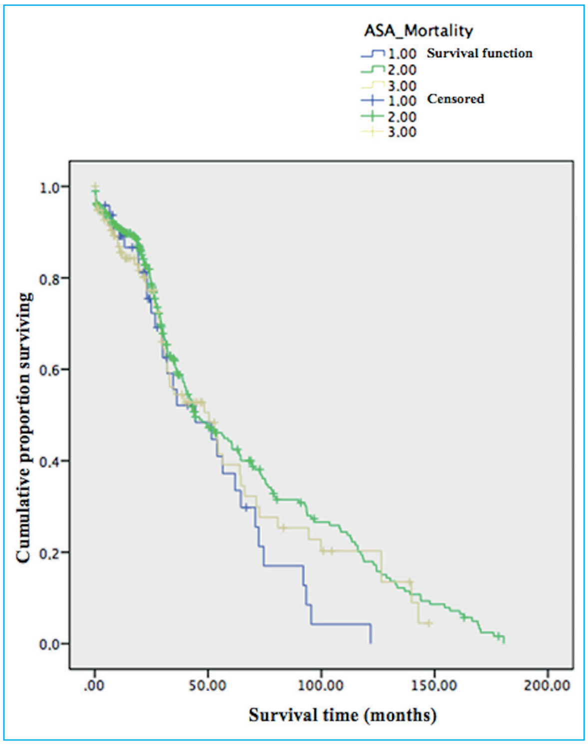

Figure 2. 5-year disease-free survival for all patients without metastatic disease.

ant limitations[18,19]. In our work, no statistical difference was observed in the three groups neither in terms of medical nor in terms of surgical complications. No difference was observed stratifying ASA class in GC patients with age < 65 years and > 65 years. Poor reliability is the main criticisms of the ASA-PS scale[20-24]. In a large single-institution study, Sankar et al[25] analyzed the agreement between ASA-PS ratings in the preoperative assessment clinic *vs.* operating theatre. The ASA-PS scale for general surgery patients had moderate inter-rater reliability, despite its inherent subjectivity. Furthermore, ASA-PS demonstrated validity as a measure of the preoperative health status, showing expected patterns of the association with patient characteristics and postoperative outcomes. The ASA-PS classification system implicitly assumes that age is unrelated to physiological fitness; but, as a matter of fact, neonates and elderly, even if healthy, are far more "fragile" in their tolerance of anesthetics compared to young adults. However, despite these limitations, the ASA-PS classification is used ubiquitously, and sometimes uncritically, to describe the patient's overall surgical condition. In our study group, age was the most significant prognostic factor, but it was previously noted as a source of disagreement in ASA-PS ratings,[21] especially because ASA-PS does not provide guidelines on how to consider age. Nonetheless, the association between age and inter-rater disagreement with Sankar et al[25] should be cautiously viewed since its statistical significance was not strong. Additionally, the association did not follow a logical pattern, such as increasing inter-rater disagreement at the extremes of age. Even surgical procedure has been previously identified as a source of disagreement, but no analysis focused on the analysis of GC patients[20,21]. For example, Haynes and Lawler[21] found that anesthesiologists assigned lower ASA-PS classes to patients undergoing minor surgical procedures than expected, even when the patients had a serious medical disease. Indeed, Saklad et al[1] stated that the ASA-PS class had "no relation to the operative procedure, so the ability of the surgeon or anesthesiologist, nor the type of anesthesia the patient will receive"[1]. Nonetheless, many anesthesiologists still consider the ASA-PS scale just an anesthetic risk predictor and not a surgical risk predictor[20]. Sankar et al[25] suggested that clinicians are less likely to agree on how some medical conditions (e.g. cancer) impact the preoperative physical status, but more likely to agree on the impact of the total burden of comorbidity. The ASA-PS had moderate ability to predict the postoperative mortality and cardiac complications, even if well assessed before surgery in an outpatient clinic. Moreover, its correlation with hospital length of stay was relatively weak, as also demonstrated in our work, likely because the hospital length of stay is influenced by many distinct clinical factors, such as age, surgery type, and hospital type (referral, university, rural, etc.). The ability of the ASA-PS scale to predict adverse outcomes has been previously observed for specific surgery types[12,26-30], where higher ASA-PS scores were associated with higher mortality rates[31,32]. ASA-PS showed modest ability to predict the postoperative cardiac complications[33,34] and, as a result, it has no importance as a postoperative mortality and morbidity predictive model[35-37]. Our work has some limitations. First, this was a retrospective cohort study from a single tertiary care center, as reflected by the high proportion of ASA 3-4 patients. Similar reports, multicentric, with differing case-mixes, are necessary to underline our findings. Secondly, our report only included patients who underwent elective gastric surgery for cancer after being assessed in an outpatient preoperative assessment clinic. Thus, the cohort excluded individuals who were treated in an emergency setting. Therefore, our findings cannot be extrapolated to non-elective surgical procedures. ASA-PS can be considered only as a component of the overall perioperative risk assessment because surgical risks vary based on patient severity and intervention type. For instance, the exposure in a high-risk patient undergoing hernia repair under local anesthesia, compared with esophagectomy or cardiac surgery in the same patient is quite different[5]. Anesthesia sometimes varies significantly in the ASA-PS classification, especially on the influence of factors such as age, anemia, obesity, and previous myocardial infarction. For these reasons, new classifications have been developed. The Charlson Comorbidity Index (CCI) was established as a method for classifying the comorbid conditions that determine mortality[38]. CCI was later identified and validated in a surgical setting as a mortality risk predictor in patients undergoing complex gastrointestinal surgery[39]. It was shown in octo-and Nonagenarians who underwent surgery for GC that these patients had higher morbidity and mortality rates associated with a CCI ≥ 5[40]. On the other hand, cancer specific survival was comparable to younger patients[40]. In another cross-sectional analysis, the only independent factor predicting mortality was the presence of comorbidity, not age[41]. By contrast, a German report, including 139 GC patients, did not find a significant correlation between CCI and postoperative morbidity and mortality[42]. In multivariate analysis the age was an independent prognostic factor for postoperative morbidity. In a series of 118 laparoscopic total gastrectomy, the male gender was independently associated with postoperative morbidity[43]. A large prospective series of 1853 patients[44] showed that overweight patients [i.e., body mass index (BMI) > 25 kg/m^2] demonstrated an increased complication rates (47.9% *vs.* 35.8%, $p < 0.001$), as anastomotic leakages (11.8% *vs.* 5.4%) and wound infections (8.9% *vs.* 4.7%). Several other investigations[45-47] have also shown the association between higher BMI and increased postoperative morbidity. Age, sex, and weight should be taken into consideration in the preoperative patient evaluation, because those factors influence the posto-perative course. Moreover, ASA-PS might underline interpretation bias and the ASA scores may be assigned depending on the assessor or factors which are taken into account[48].

Conclusions

The ASA classification is a non-specific instrument in the evaluation of the operative risk for GC patients. By definition, cancer patients have a systemic disease and should be classified as ASA 2. The practical applicability of this classification remains a challenge not only in daily practice but also in clinical research. For all these reasons and according to the results of our investigation, preoperative ASA-PS cannot serve as a direct indicator of operative risk indicator for GC patients and should be combined with other preoperative classification systems.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

For this type of study, formal consent is not required.

Human and Animal Rights Statement

All procedures followed were in accordance with the Ethical Standards of the Responsible Committee on Human Experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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