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Original Article

Role of Cardiopulmonary Exercise Testing in Predicting Perioperative Outcomes in Cancer Patients Undergoing Thoracoabdominal Surgeries; An Observational Cohort Study

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Abstract

Introduction: The cancer patients are at a high risk of developing perioperative complications. Cardiopulmonary exercise testing (CPET) is a non-invasive, perioperative risk stratification tool that predicts perioperative morbidity and mortality. Prior literature has concluded that CPET has a valuable role in predicting post-operative complications in major surgical procedures. However, the data on the effectiveness of CPET in evaluating the perioperative risk in cancer-specific populations are limited. This study assessed the usefulness of CPET in perioperative risk stratification of patients with thoracoabdominal cancer who underwent elective major thoracoabdominal surgeries. **Materials and Methods:** A retrospective observational cohort study was conducted on cancer patients that underwent pre-operative CPET at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, from September 2017 to September 2019. All adult male and female patients with a significant medical history for cancer of the thoracoabdominal region who underwent CPET before a major thoracoabdominal surgery were included in the study. **Results:** A total of 32 patients were included in the present investigation. The mean age of the sample was 62.75 ± 10.18 years, and the majority of the participants were female. Following surgery, 53% of the participants had post-operative complications in terms of morbidity and mortality. Fifteen participants had an anaerobic threshold (AT) of ≥11.0 ml/kg/min. Among these, 12 participants had an uneventful surgery. On the contrary, among 17 participants that were considered to have a high risk (<11.0 ml/kg/min) for surgery, 14 subjects (82%) had at least one complication (including mortality). The sensitivity and specificity of CPET to anticipate complications during oncological surgery were calculated to be 82% and 80%, respectively. The mean AT of participants with uneventful surgery was calculated to be 11.83 ± 1.01 ml/kg/min. This was statistically greater than the AT of subjects that had morbidity (9.86 ± 1.20 ml/kg/min) or mortality (8.95 ± 0.35 ml/kg/min) ($P < 0.001$). **Conclusion:** CPET, when using AT alone as an indicator, can provide a good-excellent prediction of perioperative outcome among oncology patients undergoing major thoracoabdominal surgical procedures.

Key words: Anaerobic threshold, maximum oxygen consumption, metabolic equivalents, morbidity, mortality

Introduction

Cancer is the leading cause of morbidity and mortality worldwide as per the World Health Organization, with approximately 14 million new cases and 8.2 million cancer-related death every year.[1] The cancer patients are at high risk for developing perioperative complications secondary to cancer disease itself and from other risk factors such as chemotherapy, radiation therapy or corticosteroids and malnourishment.[2,3] These risk factors render the pre-operative prediction of risk assessment of cancer patients convoluted.

Numerous risk stratification tools have been formulated to supplement the traditional clinical judgment for perioperative complications. These include various risk scoring systems (American Society of Anesthesiologists physical status classification, Child-Pugh classification and modified end-stage liver disease criteria), biomarkers (troponin, C-reactive protein and B-type natriuretic peptide) and subjective assessment test for determining the functional status of the patient (metabolic equivalents [METS], shuttle walk talk test and 6-min walk test).[4-9] However, these risk stratification tools have limited value in the management of complex oncological patients.[2,3]

Cardiopulmonary exercise testing (CPET) is a non-invasive, perioperative risk stratification tool, which has two main variables, anaerobic threshold (AT) and the maximum oxygen capacity (Vo_2max), which are used to predict perioperative morbidity and mortality.[10,11] AT is when anaerobic metabolism (lactic acidosis) starts in the muscles during graded exercise due to an imbalance between oxygen demand and supply. The patient begins to compensate for this physiological phenomenon through an increase in exhaled carbon dioxide (Vco_2). The Vo_2max is a maximum physiological endpoint; it is defined as the maximum capacity of an individual body to transport and use oxygen during incremental exercise.

Prior literature has concluded that CPET has a valuable role in predicting post-operative complications in cardiothoracic, liver, pancreatic and other abdominal surgeries.[12] Nonetheless, there are limited data on the effectiveness of CPET for evaluating the perioperative risk for surgeries on the cancer-specific population. Moreover, as per the authors' understanding, assessment of the usefulness of CPET in predicting perioperative risk has not been studied in the local community.

The purpose of this study was to assess the usefulness of CPET in perioperative risk stratification of patients with thoracoabdominal cancer that underwent elective major thoracoabdominal surgeries.

Materials and Methods

Study design and clinical settings

A retrospective observational cohort study was conducted on cancer patients that underwent pre-operative CPET at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, from September 2017 to September 2019. An approval from the Institutional Review Board was obtained (EXMPT-04-10-18-03).

Clinical information

All adult male and female participants with a significant medical history for cancer of the thoracoabdominal region which underwent CPET before a major thoracoabdominal surgery were included in the present investigation. In this study, we defined major surgery as a procedure requiring general anaesthesia, and during which the mesenchymal barrier was breached, an organ was partially or entirely removed, the anatomy was altered, and the participant required an overnight stay in the hospital. Subjects who were unable to complete the test, had an active cardiac condition as per the American Heart Association, or were pregnant were excluded from the study.[12]

The Hospital Information System (HIS) was used to retrieve and deidentify medical records of the subjects. Information regarding demographic data, diagnosis, type of surgery, revised cardiac index, METS, body mass index (BMI), comorbidity status and the AT was reviewed. Similarly, details of the length of stay (LOS) in the intensive care unit (ICU) or high dependency unit, length of hospital stay, delay or complications during surgery, post-operative complications and the number of mortality days were extracted from the medical record. Post-operative complications were observed using the post-operative morbidity survey tool.[13]

CPET protocol

During the CPET, all participants underwent symptom-limited incremental testing on a computer-controlled electromagnetically braked cycle ergometer under a respiratory therapist's supervision. In the beginning, each participant was given 3 min of preliminary resting period on a cycle ergometer. Their baseline measurements (such as heart rate, blood pressure and oxygen consumption [VO_2]) were established. This was followed by a 3-min warm-up period, which consisted of participant pedaling on an unloaded cycle ergometer at 0 Watts resistance. Subsequently, pedaling resistance was increased using an incremental ramp protocol at 10 Watts/min for untrained participants and 20–30 Watts/min for trained participants or those with a history of regular physical exercise. All the measurements were recorded continuously throughout the test. Participants underwent breath by breath analysis of VO_2 (till peak VO_2 was reached), carbon dioxide production, arterial oxygen tension and rating of perceived exertion (based on Modified Borg Scale). The peak VO_2 and the AT were determined by the physician using graphical and numeric findings of the test. The test was terminated if the patients started to develop chest pain or extreme shortness of breath and could not follow the protocol due to tiredness. This was in compliance with testing guidelines and is indicated due to participant safety.

AT was used for the risk stratification of the participants in the present investigation. Participants with AT of ≥11.0 ml/kg/min were classified as having a low risk for surgery, and correspondingly participants with AT of <11.0 ml/kg/min were categorised as having a high risk for surgery. Cutoff of 11.0 ml/kg/min was selected because it has previously been used by other investigators studying the role of AT in stratifying risk of surgical outcomes.[14,15]

Statistical analysis

The statistical analysis was carried out using SPSS software (version 20.0; SPSS, Chicago, IL, USA). Continuous variables were compounded as mean (± standard deviation), and categorical variables were computed as frequencies and percentages. The continuous variables were compared using a one-way analysis of variance (ANOVA) test. Overall determination for AT value was evaluated by repeated measurement ANOVA. Furthermore, regression analyses were performed by standard methods to calculate the correlation coefficient. Differences were considered to be significant at $P < 0.05$.

Results

A total of 75 charts were identified and reviewed. However, 32 participants met the inclusion and exclusion criteria of the study and underwent an oncological surgery. On the contrary, 43 participants were excluded for at least one of the following reasons; participants were unable to complete the test due to either exertional dyspnoea, chest pain, palpitations or arthritis,[4] or subjects did not proceed for surgery due to either disease progression, and the tumour was deemed irresectable by the oncological surgeon, or they were considered to have a high risk for surgery as per low AT <9.32 ml/kg/min (3).

The mean age of the sample was 62.75 ± 10.18 years, and the majority of the participants were female, 65% (n = 21). The mean BMI of the subjects was 33.12 ± 5.40 kg/m^2. In addition, 75% (n = 24) of participants had multiple comorbidities, such as ischemic heart disease, diabetes mellitus, hypertension, asthma and chronic obstructive pulmonary disorder. The metabolic equivalent was above 4 in 84.4% (n = 27) of participants [Table 1].

The most common surgical procedures performed following CPET were in the upper gastrointestinal region [Figure 1]. Around 53% (*n* = 17) of the participants had post-operative complications in terms of morbidity and mortality. The most common complications were associated with the cardiovascular system 35.4% (*n* = 6), which consisted of arrhythmias and drop in mean arterial pressure of <65 mmHg (requiring inotropic support), and respiratory system 23.5% (*n* = 4) which included of an increase in oxygen requirement during surgery and respiratory acidosis. Following surgery, 6.3% (*n* = 2) of the participants had mortality. These results are summarised in Table 2.

Fifteen participants had AT of ≥11.0 ml/kg/min. Among these, 80% (*n* = 12) had an uneventful surgery. On the contrary, among 17 participants considered to have a high risk for surgery, 82% (*n* = 14) had at least one complication (including mortality). The sensitivity and specificity of CPET to anticipate complications during oncological surgery were calculated to be 82% and 80%, respectively.

The mean AT of subjects with uneventful surgery was 11.83 ± 1.01 ml/kg/min. This was statistically greater than the AT of participants that had morbidity (9.86 ± 1.20 ml/kg/min) or mortality (8.95 ± 0.35 ml/kg/min) (*P* < 0.001).

Table 1: Baseline characteristics of the study population

Study variables	Categories	Descriptive statistic
Age (years)		62.75±10.18
Gender	Male	11 (34.4%)
	Female	21 (65.6%)
Body mass index (kg/m^2)		33.12±5.40
Comorbidity status	Single	8 (25.0%)
	Multiple	24 (75.0%)
Post-operative complications		17 (53.1%)
Metabolic equivalent	≤4	27 (84.4)
	>4	5 (15.6)
Hospital stay (days)		6.10±0.78
Intensive care unit stay (days)		1.52±0.72
Anaerobic threshold (ml/kg/min)		10.73±1.50

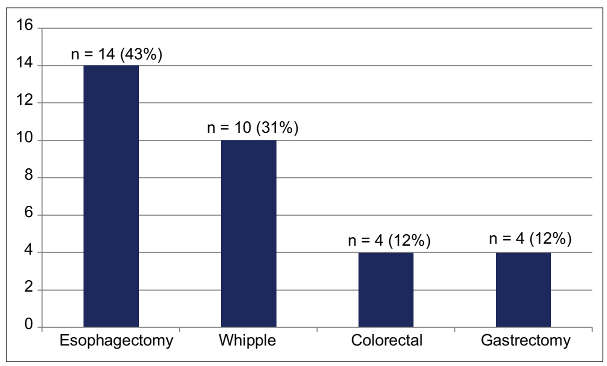

Figure 1: Procedure-wise breakdown of patients undergoing cardiopulmonary exercise testing

Table 2: Breakdown of the study population according to the anaerobic threshold

Study variables	Categories	High risk (AT value <11.0 ml/kg/min)	Low risk (AT value ≥11.0 ml/kg/min)	*P*-value
Age (years)		61.35±9.94	64.33±10.58	0.42
Gender	Male	6 (35.3%)	5 (33.3%)	0.91
	Female	11 (64.7%)	10 (66.7%)	
Body mass index (kg/m^2)		32.65±4.85	33.67±6.10	0.60
Comorbidity status	Single	4 (23.5%)	4 (26.7%)	1.00
	Multiple	13 (76.5%)	11 (73.3%)	
Post-operative complications	Absent	3 (17.6%)	12 (80.0%)	0.001
	Present	14 (82.4%)	3 (20.0%)	
Metabolic equivalent	≤4	14 (82.4%)	13 (13.3%)	1.00
	>4	3 (17.6%)	2 (86.7%)	
Hospital stay (days)		6.17±0.81	6.0±0.75	0.53
Intensive care unit stay (days)		1.47±0.72	1.57±0.75	0.71

There was a statistically significant difference present between the group of participants with AT value of <11.0 ml/kg/min and those with AT value of ≥11.0 ml/kg/min (*P* < 0.001). On the contrary, there was no statistically significant difference between age, gender, BMI comorbidity status, METS, length of hospital stay and duration of stay in the ICU [Table 2].

Discussion

This study assessed the usefulness of CPET in perioperative risk stratification of patients with thoracoabdominal cancer who underwent elective major oncological surgeries. Among 32 subjects included in the present investigation, 15 subjects were categorised as having a minimal risk (AT of ≥11.0 ml/kg/min) and 17 subjects were classified as having a high risk (AT of <11.0 ml/kg/min) for post-operative complications. The sensitivity of the CPET to predict complications during oncological surgery was calculated to be 82% and the specificity of the test was analysed to be 80%. Correspondingly, subjects with uneventful surgery had significantly higher AT than those with morbidity or mortality.

In the present study, AT was used as a single variable for CPET analysis, and the optimal cutoff value of AT of 11.0 ml/kg/min was used. Prior investigators have suggested the threshold of 11.0 ml/kg/min.[14,15] Older *et al*. conducted a study on 548 elderly patients undergoing major intra-abdominal surgery. The investigators showed that a pre-operative AT value of <11.0 ml/kg/min was associated with increased cardiovascular mortality.[14] Similarly, in a study on 106 patients undergoing elective gastric bypass surgery, Swart *et al*. reported a higher number of post-surgical complications in low AT group.[15]

In the present investigation, low AT value was associated with morbidity and mortality. These findings are similar to those reported by others.[14-17] CPET measures uptake of oxygen at increasing levels of physical work, and the test objectively determines the cardiopulmonary performance under conditions of stress (such as during surgery). Under exercise conditions, oxygen consumption becomes a linear function of cardiac output, and the measurement of aerobic capacity becomes a surrogate for the estimation of ventricular function. AT is the point at which aerobic metabolism is inadequate for maintaining high-energy phosphate production in the exercising muscles, thus forcing the anaerobic metabolism to make up the deficit. Anaerobic metabolism occurs in any tissue where oxygen delivery is inadequate to meet the energy requirement. This phenomenon has led to the concepts of 'surgical AT' and 'post-operative organ complications,' the heart's inability to meet the demand of post-operative stress.[18,19]

In the present investigation, the sensitivity and specificity of CPET were calculated to be 82% and 80%, respectively. These findings are different from those reported by other investigators. A reason for this disparity is likely to be associated with a difference in the optimal cut-point threshold that was used for the analyses. Furthermore, the cohorts on whom the investigations have been conducted are different. Snowden et al. reported a higher sensitivity (88%) and a similar specificity (79%) compared to the present study of CPET in predicting complications among patients undergoing major elective surgery. However, they used a relatively lower optimal cutoff point of AT value (10.1 ml/kg/min).[16] Similarly, Junejo *et al*. assessed CPET performance in risk stratification of patients undergoing hepatic resection. The investigators concluded that CPET had a sensitivity of 100% and a specificity of 76% in predicting complications during surgery using a cutoff value of AT of 9.9 ml/kg/min.[20]

Studies have reported that low AT may also increase unplanned stay in ICU. [20-23] Previously, Hennis et al. reported that patients with AT of more than 11.3 ml/kg/min had fewer than 3 days, whereas patients with AT of <10.4 ml/kg/min had a LOS of more than 3 days.[24] Comparing our results with Hennis *et al*., average LOS in the hospital was approximately 6 days and 1.5 days in ICU. This LOS was not a significant correlation between the extent of stay in the hospital/ICU and AT. The reason for this discrepancy in results is likely due to the difference in the study population. In the present study, all patients had thoracoabdominal carcinomas, and they underwent major elective surgical procedures with curative intent. Similarly, in the hospital where the investigation was conducted, it was a standard operating procedure of the surgical oncology to have patients stay in the hospital for an extended period (5–7 days) postoperatively following a major thoracoabdominal procedure.

A possible limitation of this study is that only AT was used for risk stratification of the subjects before the intervention. The authors were not able to include Vo2max due to the unavailability of CPET software. Nonetheless, the findings of the present study are corresponding to the investigations that have relied on both AT and Vo2max for stratifying risk among patients undergoing major surgeries. Another limitation of the study is the retrospective design. Retrospective studies are traditionally considered low quality in the hierarchy of evidence due to lack of randomisation. Due to their inherent design, they have the potential for forming false associations or magnifying positive responses. Nonetheless, in the present study, all participants' data were reviewed using the electronic HIS, and clinical findings (morbidity or mortality) from follow-up visits were cross-checked from visits of participants to different specialties.

To conclude CPET, when using AT alone, can provide a good-excellent prediction of perioperative outcomes among oncology patients undergoing major thoracoabdominal surgical procedures. Future investigations with prospective study design and large sample sizes are advocated for improving understanding and utilisation of CPET in stratifying perioperative risk among cancer patients undergoing major surgical procedures.

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Authorship Contributions

Conceived and designed the analysis: SS. Collected the data: SS, AU and SUR. Contributed data or analysis tools: SS, AWQ and ADA. Performed the analysis: SS, AU and SUR. Wrote the paper: SS, AWK and ADA.