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# CANCER PATIENTS AND MAJOR COMPLICATIONS PREDICTORS AFTER ELECTIVE ABDOMINAL SURGERY

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**Abstract**

*Patients undergoing abdominal surgery for solid tumors frequently develop major postoperative complications, which negatively affect quality of life, costs of care and survival. Few studies have identified the determinants of perioperative complications in this group.*

*We performed a prospective observational study including all patients (age > 18) undergoing abdominal surgery for cancer at a single institution between June 2015 and August 2017. Patients undergoing emergency surgery, palliative procedures, or participating in other studies were excluded. Primary outcome was composite of 30-day all-cause mortality and infectious, cardiovascular, respiratory, neurologic, renal and surgical complications. Univariate and multiple logistic regression analyses were performed to identify predictive factors for major perioperative adverse events.*

*Of a total 308 included patients, 106 (34.4%) developed a major complication during the 30- day follow-upperiod. Independent predictors of postoperative major complications were: age (odds ratio [OR] 1.03 [95% CI 1.01–1.06],p = 0.012 per year), ASA (American Society of Anesthesiologists) physical status greater than or equal to 3 (OR 2.61 [95%CI 1.33–5.17], p = 0.003), a preoperative hemoglobin level lower than 12 g/dL (OR 2.13 [95% CI 1.21–4.07], p = 0.014), intraoperative use of colloids (OR 1.89, [95% CI 1.03–4.07], p = 0.047), total amount of intravenous fluids (OR 1.22 [95% CI0.98–1.59], p = 0.106 per liter), intraoperative blood losses greater than 500 mL (2.07 [95% CI 1.00–4.31], p = 0.043), andhypotension needing vasopressor support (OR 4.68 [95% CI 1.55–27.72], p = 0.004). The model had good discrimination with the area under the ROC curve being 0.80 (95% CI 0.75–0.84, p < 0.001).*

*Our findings suggest that a perioperative strategy aimed at reducing perioperative complications in cancer surgery should include treatment of preoperative anaemia and an optimal fluid strategy, avoiding fluid overload and intraoperative use of colloids.*

**Keywords:** *Surgery, Cancer, Risk factors, Perioperative complications, Critical care*

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## INTRODUCTION:

In the last years, survival related to cancer has increased due to advances in diagnostic and therapeutic interventions, including implementation of management protocol (e.g. goal-directed hemodynamic therapy) in perioperative care. Nowadays, surgery remains the cornerstone of treatment of solid neoplasms. Unfortunately, cancer patientsare frequently characterized by a high perioperative risk because of immune system disturbances, decreased physiologic reserves, and long duration of procedures, with significant fluid and blood losses. Previous studies showed worse postoperative outcomes in this subgroup of patients, including higher mortality rates, increased costs and longer hospital and intensive care unit (ICU) length of stay. Furthermore, perioperative complications negatively affect quality of life and may delay or preclude further cancer treatment, such as adjuvant chemotherapy. Therefore, preventing complications in this specific group of patients is of particular importance (Barthlen et al., 2017).

Identification of predictive factors for complications is critical for several reasons. First of all, it allows a more accurate risk stratification and hence adequate planning of perioperative management. In addition, modifiable factors could become target for tailored interventions aimed at reducing postoperative complications. Finally, identification of predictive factors helps to identify areas for future investigations. As of today, few studies focused on identifying predicting factors for perioperative complications in cancer patients undergoing abdominal surgery. Accordingly, we designed and performed a prospective observational study aimed at identifying predictive factors for major complications including mortality in patients undergoing elective abdominal surgery for cancer (Bhagvat et al., 2017).

## *2.0 Methods*

We designed a prospective observational study including cancer patients undergoing elective abdominal surgery between June 2015 and August 2017. The study was approved by the Ethics Committee and written informed consent obtained from every patient. Patients were included if they met all the following criteria: age greater than 18 years, diagnosis of a solid neoplasm, plan for elective open abdominal surgery with curative intent or bowel reconstruction from previous primary tumor excision, and written informed consent. The exclusion criteria were patient denial, emergency surgeries, participation in other studies and admission for palliative procedures.

### *Anesthetic and surgical management*

All patients were anesthetized according to the standard institutional protocol for high-risk surgery. Synthetic colloids were used (6% hydroxyethyl starch 130/0.4) in patients with no previous renal dysfunction, coagulopathy or infection (Bhagvat et al., 2017).

### *Data Collected*

For the description of baseline characteristics and the demographics of patients, demographics of patients, including comorbidities, health-related Quality-of-Life, oncological diagnosis and status of disease the data were collected at baseline. Intraoperative data included type of surgery, therapeutic interventions and complications. Patients were followed up daily after surgery for30 days by four trained physicians, each with more than2 years-experience of postoperative care. Clinical outcomes were evaluated during the intensive care unit (ICU) stay and then on the general ward. In case of hospital discharge before day 30, a follow-up phone call was performed by two physicians. Those who conducted the follow-up telephone assessment shad no participation in the perioperative care and had no access to the database. We used a standardized questionnaire to evaluate outcomes after hospital discharge, assessing clinical complications, vital status and quality of life (Bhagvat et al., 2017).

### *Outcomes*

The basic outcome was the composite endpoint of 30-daymortality and major complications defined as infectious, cardiovascular, respiratory, neurologic, renal and surgical complications. All complications were defined according to standard criteria for details on outcome definitions. Secondary outcomes were Health Related Quality of Life (HRQoL) 30 days after surgery, ICU and hospital length of stay.

### *Statistical Analysis*

The results are expressed as the means with standard deviation (SD) or medians with interquartile ranges (IQRs) as appropriate. Normality was assessed with the Kolmogorov-Smirnov test. Univariate associations between potential risk factors and complications were assessed using the chi-square test, Fisher's exact test, likelihood ratio test, t-test or Mann-Whitney U test. A forward multiple logistic regression analysis was then performed to estimate independent predictive factors for complications. This model included risk factors that were identified by univariate analysis ($p < 0.05$) plus the following clinically relevant data, presence of metastatic disease and HRQoL evaluation (utilities and VAS scores) (Bozzay, Broce and Mousa, 2016).

To evaluate the stability of the effect estimates, bootstrap was applied for 1000 samples. All variables that remained significant after the bootstrap procedure were kept in the model. A receiver operating characteristic (ROC) curve was constructed, and the area under the ROC curve (AUC) determined to assess the discriminant ability of the multiple logistic regression models to predict complications. A value of less than 0.05 was considered to indicate statistical significance (p), and all tests were two-tailed. Statistical analyses were performed using SPSS.

## RESULTS:

A total of 927 patients were assessed for eligibility according to Figure S1. After exclusions, a total of 308 patients were enrolled in the study. Tables 1 and 2 describe baseline characteristics of the patients and type of performed surgical procedures. Most operations were colorectal and gynecological procedures. Regional anesthetic technique combined with general anesthesia was performed in 80% of patients. A total of 166 (53.9%) patients were admitted to the ICU following surgery.

**Table 1** Baseline characteristics of the patients and preoperative laboratory findings

| Variable | Total | Complications | | |
|---|---|---|---|---|
| | | No | Yes | |
| | *n* = 308 (100%) | *n* = 202 (66%) | *n* = 106 (34%) | |
| Age (years), mean and standard deviation | 59.7 ± 14.1 | 57.8 ± 14.5 | 63.3 ± 12.5 | 0.010 |
| BMI (kg/m$^2$), median (IQR) | 25.6 (22.3–29.5) | 25.9 (22.7–30.1) | 25.3 (21.9–28.2) | 0.066 |
| Male gender | 139 (45.1%) | 87 (43.1%) | 52 (49.0%) | 0.316 |
| Preoperative ambulatory reevaluation | 31 (10.1%) | 17 (8.4%) | 14 (13.2%) | 0.184 |
| Functional status (<4METs) | 76 (24.7%) | 36 (17.8%) | 40 (37.7%) | < 0.001 |
| Systemic arterial hypertension | 147 (47.7%) | 93 (43.0%) | 54 (51.0%) | 0.413 |
| Chronic obstructive pulmonary disease | 34 (11%) | 20 (9.9%) | 14 (13.2%) | 0.379 |
| Tobacco use | 29 (9.4%) | 19 (9.4%) | 10 (9.4%) | 0.994 |
| Coronary arterial disease | 20 (6.5%) | 8 (4.0%) | 12 (11.3%) | 0.013 |
| Heart failure | 25 (8.1%) | 11 (5.4%) | 14 (13.2%) | 0.018 |
| Diabetes mellitus | 53 (17.2%) | 29 (14.3%) | 24 (22.6%) | 0.067 |
| Chronic renal disease | 66 (21.4%) | 32 (15.8%) | 34 (32.0%) | 0.001 |
| Previous stroke | 12 (3.9%) | 5 (2.5%) | 7 (6.6%) | 0.075 |
| Karnofsky Performance Status Scale Score (< 70%) | 9 (2.9%) | 4 (2.0%) | 5 (4.7%) | 0.283 |
| Previous oncologic treatment | 148 (48.1%) | 95 (47.0%) | 53 (50.0%) | 0.620 |
| Metastatic disease | 55 (17.9%) | 35 (17.3%) | 20 (18.8%) | 0.737 |
| Preoperative abnormal EKG | 67 (21.8%) | 39 (19.3%) | 28 (26.4%) | 0.151 |
| Hemoglobin (< 12 g/dL) | 94 (30.5) | 52 (25.7%) | 42 (39.6%) | 0.012 |
| ASA physical status (≥3) | 62 (20.1%) | 28 (13.8%) | 34 (32.0%) | < 0.001 |
| Sodium (< 135 mEq/L) | 16 (5.2%) | 7 (13.5%) | 9 (8.5%) | 0.059 |
| Potassium (< 3.5 or > 5.0 mEq/L) | 34 (11%) | 22 (11.0%) | 12 (11.3%) | 0.909 |
| Systolic pressure (mmHg), median (IQR) | 127 (112–140) | 129 (113–142) | 125 (111–138) | 0.134 |
| Diastolic pressure (mmHg), median (IQR) | 80 (71–88) | 80 (72–90) | 80 (71–86) | 0.194 |
| Heart rate (bpm), median (IQR) | 77 (67–89) | 76 (67–89) | 78 (67–89) | 0.482 |
| Creatinine (mg/dL), median (IQR) | 0.84 (0.73–1.00) | 0.82 (0.72–0.95) | 0.87 (0.74–1.12) | 0.020 |
| Platelets (10$^3$ cells/mm$^3$), median (IQR) | 234 (193–292) | 233 (193–286) | 239 (192–303) | 0.686 |
| EQ-5D-3 L | 0.84 (0.72–0.88) | 0.87(0.73–0.88) | 0.81(0.67–0.88) | 0.063 |
| VAS | 80 (60–90) | 80(70–90) | 70(60–87.5) | 0.081 |

Source: (Han, Wang and Chen, 2018)

**Table 2** Surgical characteristics of the study patients

| Variable | Total | Complications | | P |
|---|---|---|---|---|
| | | No | Yes | |
| | $n = 308$ | $n = 202$ (66%) | $n = 106$ (34%) | |
| Type of procedure | | | | < 0.001 |
| Colorectal surgery | 100 | 66 (66%) | 34 (34%) | |
| Hysterectomy and/or anexectomy | 57 | 50 (88%) | 7 (12%) | |
| Gastrectomy | 27 | 17 (63%) | 10 (37%) | |
| Liver resection | 25 | 17 (68%) | 8 (32%) | |
| Pancreatic surgery | 22 | 11 (50%) | 11 (50%) | |
| Exploratory laparotomy | 22 | 16 (73%) | 6 (27%) | |
| Bowel resection | 13 | 10 (76.9%) | 3 (23.1%) | |
| Esophagectomy | 11 | 0 (0%) | 11 (100%) | |
| Colon reconstruction | 11 | 9 (81.8%) | 2 (18.2%) | |
| Cystectomy | 9 | 2 (22.2%) | 7 (77.8%) | |
| Peritonectomy | 5 | 0 (0%) | 5 (100%) | |
| Biliary-enteric anastomosis | 3 | 2 (66.7%) | 1 (33.3%) | |
| Cytoreduction | 3 | 2 (66.7%) | 1 (33.3%) | |

Source: (Han, Wang and Chen, 2018)

One hundred and six (34%) patients had at least one major complication according to Table 3. A total of 32 patients (10.4%) had at least two complications. At 30 days, death occurred in 7 patients (2.3%), respiratory complications in 14 (4.5%), cardiovascular in 28 (9.1%), infectious in 17 (5.5%), renal in 40 (13.0%) and surgical in 29 (9.4%) patients (Table 4).

**Table 3** Postoperative complications during the 30-day follow-up period

| Outcomes | *n* (%) |
|---|---|
| Respiratory complications | 14 (4.5%) |
| Acute respiratory failure | 5 (1.6%) |
| Pneumonia | 13 (4.2%) |
| Prolonged mechanical ventilation (> 48 h) | 14 (4.5%) |
| Cardiovascular complications | 28 (9.1%) |
| Acute myocardial infarction | 4 (1.3%) |
| Cardiogenic shock | 23 (7.5%) |
| Stroke | 2 (0.6%) |
| Infectious complications | 17 (5.5%) |
| Septic shock | 14 (4.5%) |
| Severe sepsis | 17 (5.5%) |
| Acute kidney injury | 40 (13.0%) |
| Surgical complications | 29 (9.4%) |
| Anastomosis dehiscence | 12 (3.9%) |
| Operative wound dehiscence | 3 (1.0%) |
| Surgical wound infection | 11 (3.6%) |
| Re-operation | 17 (5.5%) |
| Death | 7 (2.3%) |
| Septic shock (pulmonary origin) | 1 (0.3%) |
| Septic shock (abdominal origin) | 4 (1.3%) |
| Septic shock (multiple origin) | 2 (0.6%) |

Source: (Han, Wang and Chen, 2018)

**Table 4** Table describing intra-operative events and postoperative complications

| Intraoperative variables | | | |
|---|---|---|---|
| Regional anaesthesia | 159 (78.7%) | 86 (81.1%) | 0.617 |
| Use of colloids (HES 6%) | 96 (47.5%) | 72 (68.0%) | 0.001 |
| Use of continuous vasopressors | 4 (2.0%) | 24 (22.6%) | < 0.001 |
| Intraoperative fluid volume (L), median (IQR) | 3.1 (2.5–4.5) | 5.0 (3.5–6.5) | < 0.001 |
| Red blood cell transfusion | 7 (3.5%) | 21 (19.8%) | < 0.001 |
| Estimated bleeding (> 500 mL) | 38 (18.8%) | 50 (47.1%) | < 0.001 |
| Surgical length (min), median (IQR) | 247 (166–331) | 315 (220–385) | < 0.001 |

Source: (Han, Wang and Chen, 2018)

The group of patients who developed complications was older (63.3 ± 12.5 years vs. 57.8 ± 14.5 years, p < 0.001),had a higher prevalence of poor preoperative functional status, defined by less than 4 metabolic equivalents(METS) (37.7% vs. 17.8%, p < 0.001), had a higher prevalence of coronary artery disease (11.3% vs. 4.0%, p = 0.013),heart failure (13.2% vs. 5.4%, p = 0.018) and chronic kidney disease (32% vs. 15.8%, p = 0.001) (Table 1). The incidence of metastatic disease was similar between groups. The occurrence of preoperative anemia (hemoglobin lower than 12 g/dL) was higher in the group with complications compared to the group without complications (39.6% vs. 25.7%, p = 0.012), as the number of patients with an ASA score equal to or greater than 3(32.0% vs 13.8%, p < 0.001).There was no difference between groups in the preoperative Health Related Quality of Life (HRQoL) and in the VAS values (Table 1).

Patients who developed major complications, when

compared to patients without complications, were more likely to receive colloids (68.0% vs. 47.5%, p = 0.001), to receive vasopressors due to hypotension (22.6% vs. 2.0%,p < 0.001), and higher amount of intravenous fluid [5.0 L(IQR 3.5–6.5) vs 3.1 L (2.5–4.5), p < 0.001] intra operative. Additionally, patients who developed major complications had a higher incidence of intraoperative bleeding (47.1% vs. 18.8%, p < 0.001) and were more exposed to red blood cell transfusions (19.8% vs 3.5%,p < 0.001) and had longer duration of surgery [315 min(220–385) vs. 247 min (166–331), p < 0.001) (Table 4).

In a sample of 191 patients, health-related quality-of life decreased in both groups. On the other hand, VAS did not change (Table 5).In the forward multiple logistic regression model, age, ASA physical status, preoperative anemia, use of colloids, blood losses and hypotension requiring intraoperative vasopressors were independently related to complications (Table 6).

**Table 5** Health-related quality-of-life evaluated through EQ-5D-3 L and VAS

| | Preoperative (n = 191) | Postoperative (n = 191) | P* |
|---|---|---|---|
| EQ5D | 0.87 (IQR 0.78–1.00) | 0.83 (IQR 0,72–0,88) | 0.001 |
| VAS | 80 (IQR 70–90) | 80 (IQR 70–90) | 0.577 |

Source: (Han, Wang and Chen, 2018)

**Table 6** Results of multiple logistic regression analysis to determine predictive factors for major complications following cancer surgery

| Variable | Odds ratio (CI 95%) | P |
|---|---|---|
| Age (years) | 1.03 (1.01–1.06) | 0.010 |
| ASA physical status (≥3) | 2.61 (1.34–5.49) | 0.004 |
| Preoperative hemoglobin (< 12 g/dL) | 2.13 (1.15–4.15) | 0.016 |
| Use of colloids | 1.89 (0.99–3.75) | 0.049 |
| Estimated blood loss (> 500 mL) | 2.06 (0.97–4.42) | 0.048 |
| Intraoperative hypotension requiring vasopressor | 4.67 (1.41–15.48) | 0.004 |

Source: (Han, Wang and Chen, 2018)

## DISCUSSION:

In our prospective observational study, we found that, in cancer patients undergoing abdominal surgery, age, ASA score, preoperative anemia and intraoperative bleeding, use of colloids, higher amount of fluids and vasopressors were identified as predictors of major postoperative complications including mortality. Excluding age and ASA score, all of the factors identified in our study are modifiable (Bozzay, Broce and Mousa, 2016).

These findings suggest that a perioperative strategy based on the treatment of preoperative anemia, implementation of conservative blood management and effective bleeding control and hemodynamic management during surgery may improve outcomes in patients undergoing elective major oncologic abdominal surgery. Preoperative anemia has been associated with worse outcomes in surgical patients (Gapany, 2016).

Anemia in cancer patients is common and multi factorial. Blood loss, decreased bone marrow production, increased destruction of red blood cells and drug toxicities are involved in cancer-related anemia. In a retrospective study that preoperative anemia was associated with postoperative 30-day mortality and cardiovascular events in patients undergoing major non-cardiac surgery. It is analyzed that an increased risk of death and cardiovascular complicationsin the postoperative period in patients with preoperative anemia, particularly in patients with previous cardiovascular disease. According to another description the prospective study demonstrated that low preoperative hematocrit levels were associated with an increased incidence of pneumonia, hospital length of stay and mortality. Moreover, preoperative anemia is also a known risk factor for postoperative anemia and increased requirements for perioperative blood transfusion, which contribute to postoperative complications (Han, Wang and Chen, 2018).

Preventive strategies for patients with preoperative anemia may enhance postoperative outcomes. The use of preoperative recombinant human erythropoietin in cancer patients appears to be safe, although previous studies have associated its use with

the progression of disease and mortality. A recent pilot study in patients undergoing cardiac surgery suggested that preoperativere blood cell transfusion reduced the intraoperative requirements for additional transfusion and decreased postoperative organ failure. Despite all complications related to transfusion in cancer patients undergoing abdominal surgeries, this group of patients may benefit from postoperative liberal transfusion strategies (Han, Wang and Chen, 2018).

This study also identified that the use of the colloidsstarches in the intraoperative period is an independent factor associated with postoperative complications. Although it was not possible to establish causal effects because of our study design, recent studies have shown an increased risk of renal dysfunction and mortality in patients with sepsis related to the use of artificial colloids such as starches. Hypotension requiring a vasopressor during surgery was identified in our study as an independent factor predicting a poor outcome after surgery. Cancer surgery is often characterized by long and extensive resection with excessive blood losses, ischemia and reperfusion injuries and exposure to blood transfusion. All of these factors can lead to an exacerbated systemic inflammatory response syndrome (SIRS) and vasodilator shock. SIRS-related cardiovascular failure has been shown to be associated with postoperative organ failure, severe complications and mortality (Han, Wang and Chen, 2018).

Our study reported that older age and a higher ASA status were independent characteristics associated withpostoperative complications. The relationship between age and co-morbidities with poor outcomes after surgery has been well described in previous studies. The worldwide demographic transition, particularly in developing countries, has led to an increase in the number of patients older than 65 years undergoing major surgery, with higher operative mortality. In our study, the mean age of the group of patients with severe complications was 63.3 years-old, which was 7 years older than the group without complication. The physiologic reserve declines with age and explain why older patients have a reduced tolerance for major oncologic resections(Han, Wang and Chen, 2018).

## CONCLUSION:

In conclusion, this study suggests that a higher age and ASA score, preoperative anemia, intraoperative blood losses, intraoperative hypotension requiring vasopressors, and the administration of artificial colloids in patients undergoing major abdominal cancer surgery were independently associated with severe complications and death. These findings suggest that a perioperative management strategy based on the treatment of preoperative anemia, implementation of hemostatic surgical techniques, conservative blood management, and adequate hemodynamic control avoiding hypotension might reduce severe complications in this population. Future randomized studies aiming at improving perioperative outcome in cancer patients should focus on optimizing these aspects.

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