

Associations Between Malignancy and Cardiovascular Complications Following Emergency Laparotomy – a Retrospective Cohort Study

Rasmus Peuliche Vogelsang (✉ Rvo@regionsjaelland.dk)

Zealand University Hospital Koge: Sjaellands Universitetshospital Koge <https://orcid.org/0000-0003-0081-5093>

Jacob Hartmann Søby

Zealand University Hospital Koge: Sjaellands Universitetshospital Koge

Mai-Britt Tolstrup

Herlev Hospital

Jakob Burcharth

Zealand University Hospital Koge: Sjaellands Universitetshospital Koge

Sarah Ekeløf

Zealand University Hospital Koge: Sjaellands Universitetshospital Koge

Ismail Gögenur

Zealand University Hospital Koge: Sjaellands Universitetshospital Koge

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Abstract

Background

Several studies have shown a possible causal relationship between the occurrence of systemic inflammation in patients with malignant disease and increased risk of cardiovascular events. Our objective was to estimate the association between malignant disease and postoperative cardiovascular complications. Secondly, we aimed to identify risk factors for postoperative cardiovascular complications.

Methods

We conducted a retrospective cohort study of all patients ≥ 18 years undergoing emergency laparotomy between 2010 and 2016 at the Department of Surgery at Zealand University Hospital, Denmark. Complications were graded according to the Clavien-Dindo (CD) classification of surgical complications. A multivariate logistic regression analysis was performed to estimate the association between malignant disease and cardiovascular complications within 30 days of emergency laparotomy and to identify other risk factors for postoperative cardiovascular complications after emergency laparotomy.

Results

We identified 1188 patients ≥ 18 years undergoing emergency laparotomy between 2010 and 2016, in which 254 (21%) had malignant disease. Within 30 days of emergency laparotomy, 89 (9.5%) of patients without malignancy died, as compared with 45 (18%) of patients with malignancy ($p < 0.001$). Severe cardiovascular complication graded CD 3–5 occurred in 93 (8%) of all patients within 30 days of emergency laparotomy. We found no association between malignancy and postoperative cardiovascular complications. Increasing age and ASA physical status classification system (ASA) score \geq III were the only independent risk factors of cardiovascular complications graded CD 3–5.

Conclusions

Malignancy was not associated with postoperative cardiovascular complications after emergency laparotomy. Risk factors for major cardiovascular complications after emergency abdominal surgery were age and ASA score \geq III.

Introduction

Postoperative surgical and medical complications are common following emergency laparotomy, and perioperative cardiovascular events are the leading cause of morbidity and mortality after non-cardiac surgery.^{1,2} Patient age, male sex, and chronic medical conditions such as ischemic heart disease,

peripheral vascular disease, diabetes, and renal insufficiency are independent preoperative predictors of myocardial injury after non-cardiac surgery.³ The surgical stress response associated with surgery and anesthesia is characterized by activation of the sympathetic nervous system with a rise in catecholamines, systemic inflammation, and immune dysfunction, all of which may trigger cardiovascular complications.^{2,4} Systemic inflammation, which is the main defining characteristics of the surgical stress response, has also been suggested as an essential promoter of acute coronary syndrome and cardiac arrhythmia.⁵⁻⁸ Similarly, the importance of the inflammatory response as an enabling characteristic of cancer has become increasingly recognized in recent years.⁹ On tumor level, necrosis and tumor products cause the release of pro-inflammatory cytokines such as IL-6, IL-1, TNF- α and interferons.¹⁰ We hypothesized that systemic inflammation, based on present malignant disease, increased the risk of postoperative cardiovascular events in patients undergoing emergency abdominal surgery.

The objective of this study was to determine the relationship between malignancy and postoperative cardiovascular complications. Secondly, we aimed to identify other potential risk factors for cardiovascular complications after emergency laparotomy.

Methods

We conducted a retrospective cohort study at the general surgery department at Zealand University Hospital, Denmark. All patients with emergency admission to the emergency department and scheduled for any emergency gastrointestinal surgical procedure from January 2010 to October 2016 were included in the cohort. We only included adults ≥ 18 years undergoing emergency laparotomy. A detailed description of the data collection can be found elsewhere.¹¹ Briefly, data extraction was obtained from electronic medical journals covering the time from admission to 30 days after surgery. We extracted pre-, per- and postoperative variables including age, weight, height, tobacco use, alcohol consumption, comorbidities, malignancy status, prescription medicine, oncological treatment within eight weeks prior to surgery, information on the surgical procedure, postoperative complications, and 30-day mortality. WHO Performance Status was defined as the patient's level of function and capacity for self-care, according to ECOG/WHO classification.¹² ASA score was graded according to the American Society of Anesthesiologists physical status classification system. Body mass index (BMI) was defined as kg/m^2 . Alcohol consumption was classified according to the recommendations provided by the Danish Health Authority, where weekly use is recommended not to exceed seven units for women and 14 units for men. Comorbidities were registered if being medically treated at the time of admission or if prior treatment was described in the admission journal.

We constructed a composite malignancy variable consisting of any diagnosis of active malignancy at admission or any ICD-10 codes with a diagnosis of cancer (ICD-10 C0-97) or any perioperative finding of malignancy. Patients with a diagnosis of non-melanoma skin cancer were not included in the malignancy group. All patients undergoing laparoscopic procedures were excluded. Any laparoscopic procedure converted to laparotomy was classified as laparotomy. Postoperative complications were graded

according to the Clavien-Dindo Classification of Surgical Complications.^{13,14} Complications were defined as any deviation from the ordinary postoperative course and ranked 1–5 according to the severity and treatment required. Complications ranked 3–5 were severe adverse cardiovascular events composed of either organ dysfunction, the requirement of surgery or percutaneous coronary intervention, intermediate or intensive care, or death. The primary outcome was cardiovascular complication Clavien-Dindo grade 3–5.

Data were presented as frequencies and percentages for categorical variables and mean with standard deviation (SD) for continuous variables. To identify risk factors for cardiovascular complications graded 3–5 on the Clavien-Dindo score, we performed a multivariate logistic regression analysis on all complete cases with the predefined clinically relevant variables: age in ten-year increments, sex, WHO performance status ≥ 2 , ASA score \geq III, current smoking, weekly alcohol consumption above the threshold recommended by the Danish Health Authority, comorbidity in the form of malignancy, diabetes, cerebrovascular disease, hypertension, ischemic heart disease, chronic nephropathy, the use of statins, immune modulation therapy, and anticoagulation therapy. Odds ratios (OR) with 95% confidence intervals (CI) were given and considered statistically significant if $p < 0.05$. We assessed multicollinearity with variance inflation factor analysis. A factor higher than 1.5 was subjected to further analysis. The goodness of fit was estimated with McFadden's R² test. Analyses were performed using the statistical software RStudio (ver. 3.5.1), including the packages tidyverse, tableone, icd, and sjPlot. The study was approved by the Region of Zealand on behalf of the Danish Data Protection Agency (approval number REG-028-2019). Informed consent was not required, according to Danish law. All reporting was done in accordance with the STROBE statement.¹⁵

Results

In total, we included 1188 patients ≥ 18 years undergoing laparotomy on acute admission to the surgical emergency department between 2010–2016. See Fig. 1 for a flowchart of the patient selection process. Patient mean age was 65 (SD 16.3) years, and 53.7% were female. Mean BMI was 25 (SD 5.7) kg/m². ASA score was \geq III in 31.1%, and WHO Performance Status was ≥ 2 in 8.9% of the population. Overall, 31.1% of patients were current smokers, and 11.2% had a weekly intake of alcohol higher than recommended by The Danish Health Authority. At the time of admission, 29.4% of the population received anticoagulant therapy, 20.2% received statins, and 12.3% received immune modulation therapy. A total of 1.8% of the patients have had oncological treatment within eight weeks before surgery. Of patients undergoing emergency laparotomy, 254 (21.4%) had a present malign disease. Of these, 43 (16.9%) had disseminated malignant disease. The group of patients with malignant disease was older, had a higher ASA score, and WHO Performance Status compared with patients without malignant disease. The frequencies of obstructive pulmonary disease and ischemic heart disease were lower in the malignant group. See Table 1 for an additional comparison of demographics, comorbidities, and medication between patients with or without present malignancy.

Table 1
Demographics of Patients Undergoing Emergency Laparotomy.

	No malignancy (n = 934)	Malignant disease, not disseminated (n = 211)	Disseminated malignant disease (n = 43)	Total (n = 1188)	Missing (%)
Age, n (SD)	63.4 (16.8)	71.1 (13.1)	68.4 (9.7)	64.9 (16.3)	0.0
Age group, n (%)					0.0
<40	83 (8.9)	7 (3.3)	0 (0.0)	90 (7.6)	
40–49	120 (12.8)	3 (1.4)	1 (2.3)	124 (10.4)	
50–59	147 (15.7)	19 (9.0)	7 (16.3)	173 (14.6)	
60–69	198 (21.2)	61 (28.9)	12 (27.9)	271 (22.8)	
70–79	220 (23.6)	58 (27.5)	18 (41.9)	296 (24.9)	
80–89	143 (15.3)	55 (26.1)	5 (11.6)	203 (17.1)	
>90	23 (2.5)	8 (3.8)	0 (0.0)	31 (2.6)	
Female sex, n (%)	502 (53.7)	115 (54.5)	21 (48.8)	638 (53.7)	0.0
BMI, n (SD)	25.5 (5.8)	25.4 (5.4)	23.1 (4.6)	25.4 (5.7)	36.3
BMI group, n (%)					36.3
<18.5	50 (8.4)	10 (7.5)	5 (16.7)	65 (8.6)	
18.5–30	435 (73.4)	102 (76.1)	22 (73.3)	559 (73.8)	
>30	108 (18.2)	22 (16.4)	3 (10.0)	133 (17.6)	
Smoking status, n (%)					6.2
Non-smoker	415 (47.7)	96 (47.8)	24 (55.8)	535 (48.0)	

	No malignancy (n = 934)	Malignant disease, not disseminated (n = 211)	Disseminated malignant disease (n = 43)	Total (n = 1188)	Missing (%)
Former smoker	175 (20.1)	47 (23.4)	10 (23.3)	232 (20.8)	
Smoker	280 (32.2)	58 (28.9)	9 (20.9)	347 (31.1)	
Weekly alcohol intake, n (%) ^a	98 (11.1)	23 (11.5)	5 (11.6)	126 (11.2)	5.5
ASA score, n (%)					10.9
I	153 (18.6)	33 (17.0)	0 (0.0)	186 (17.6)	
II	441 (53.7)	96 (49.5)	6 (14.0)	543 (51.3)	
III	199 (24.2)	61 (31.4)	27 (62.8)	287 (27.1)	
IV-V	28 (3.4)	4 (2.1)	10 (23.3)	42 (4.0)	
WHO performance status, n (%)					4.7
0	630 (70.6)	124 (61.7)	19 (48.7)	773 (68.3)	
1	194 (21.7)	49 (24.4)	15 (38.5)	258 (22.8)	
2	47 (5.3)	22 (10.9)	5 (12.8)	74 (6.5)	
3-4	21 (2.4)	6 (3.0)	0 (0.0)	27 (2.4)	
Diabetes, n (%)	94 (10.2)	32 (15.2)	4 (9.3)	130 (11.1)	1.2
Cerebrovascular disease, n (%)	85 (9.2)	18 (8.5)	4 (9.3)	107 (9.1)	1.0
Hypertension, n (%)	125 (13.6)	27 (12.9)	8 (18.6)	160 (13.6)	1.1
Ischemic heart disease, n (%)	108 (11.7)	22 (10.4)	3 (7.0)	133 (11.3)	1.1
Obstructive pulmonary disease, n (%)	145 (15.7)	28 (13.3)	8 (18.6)	181 (15.4)	0.8

	No malignancy (n = 934)	Malignant disease, not disseminated (n = 211)	Disseminated malignant disease (n = 43)	Total (n = 1188)	Missing (%)
Chronic nephropathy, n (%)	23 (2.5)	13 (6.2)	2 (4.7)	38 (3.2)	1.0
Cirrhosis of liver, n (%)	16 (1.7)	2 (0.9)	1 (2.3)	19 (1.6)	1.0
Statins, n (%)	184 (19.8)	48 (22.9)	7 (16.3)	239 (20.2)	0.3
Immune modulation therapy, (%)	118 (12.7)	19 (9.0)	9 (20.9)	146 (12.3)	0.3
Anticoagulant therapy, n (%)	264 (28.4)	69 (32.9)	15 (34.9)	348 (29.4)	0.3
Oncological treatment within 8 weeks, (%)	3 (0.3)	4 (1.9)	14 (32.6)	21 (1.8)	0.8

In total, 15.0% of all patients had a cardiovascular complication within 30 days following emergency laparotomy. Cardiovascular complications graded 1–2 and 3–5 on the Clavien-Dindo score occurred in 7.2% and 7.8% of the total population, respectively. See Table 2 for all 30-day clinical outcomes. Of all available cases, 961 cases (81%) had complete information on all variables and were included in the multivariate logistic regression analysis. We found no significant association between present malignant disease and cardiovascular complications graded 3–5 on the Clavien-Dindo score within 30 days of emergency laparotomy (OR 0.8, 95% CI; 0.4, 1.5). The only variables which significantly increased the odds ratio for postoperative cardiovascular complications graded 3–5 on the Clavien-Dindo score were increasing age in 10-year increments (OR 1.6, 95% CI; 1.3, 2.0) and ASA score above three (OR 2.0, 95% CI; 1.2, 3.3). See Table 3 for all variables included in the multivariate logistic regression analysis.

Table 2
30-day Outcomes after Emergency Laparotomy Stratified by Malignancy Status.

	No malignancy (n = 934)	Malignant disease, not disseminated (n = 211)	Disseminated malignant disease (n = 43)	Total (n = 1188)
Cardiovascular complication	140 (15.0%)	30 (14.2%)	8 (18.6%)	178 (15.0%)
Cardiovascular complication CD 1–2	66 (7.1%)	15 (7.1%)	4 (9.3%)	85 (7.2%)
Cardiovascular complication CD 3–5	74 (7.9%)	15 (7.1%)	4 (9.3%)	93 (7.8%)
Cardiac death	17 (1.8%)	4 (1.9%)	1 (2.3%)	22 (1.9%)
Overall mortality	89 (9.5%)	30 (14.2%)	15 (34.9%)	134 (11.3%)

Table 3
Multivariate Logistic Regression Model for 30-day Postoperative Cardiovascular Complications.

	Cardiovascular complications graded 3–5 on the Clavien-Dindo score		
	<i>Odds Ratio</i>	<i>CI</i>	<i>p-value</i>
Age ^(a)	1.64	1.33–2.04	< .001
Sex (male)	1.01	0.60–1.68	0.98
WHO Performance Status \geq 2	1.17	0.54–2.37	0.67
ASA score \geq III	1.96	1.15–3.34	0.01
Current smoking	1.17	0.66–2.03	0.60
Weekly alcohol intake ^(b)	1.41	0.62–2.90	0.38
Malignancy	0.80	0.43–1.42	0.46

Within 30 days of surgery, 134 (11.3%) patients died. Of these, 22 patients died due to cardiovascular complications, representing 16% of all deaths. Of patients with malignant disease, 45 (17.7%) died within 30 days of surgery. Stratified by malignancy status, 30 out of 211 (14.2%) patients with non-disseminated malignancy died, and 15 out of 43 patients (34.9%) patients with disseminated malignant disease died within 30 days of surgery.

Discussion

With this study, we aimed to investigate the association between cardiovascular complications following emergency laparotomy and the presence of malignant disease. We found no significant association between present malignant disease and cardiovascular complications graded 3–5 on the Clavien-Dindo score within 30 days of emergency laparotomy. Risk factors associated with cardiovascular complications graded 3–5 on the Clavien-Dindo score were increasing age, and ASA score above three.

In this cohort of patients undergoing emergency laparotomy, cardiovascular complications were common (15.0%) and were the cause of death in one out of seven patients who died within 30 days of surgery. In addition, we found malignant disease to be a prominent driver of postoperative mortality, highlighting the need for targeted interventions in this group of high-risk patients. The literature examining the cardiovascular outcome of surgical patients is diverse; however, studies targeting specific subgroups of patients and procedures are lacking. In a previous study on the association between postoperative troponin levels and 30-day mortality including 15 133 patients undergoing elective and urgent non-cardiac surgery, the authors did not find an association between vascular death and active malignancy as compared with patients without active malignancy (hazard ratio 1.14; 95% CI, 0.72 to 1.79).¹⁶ This is in line with the findings of the current study. In another study of 875 patients with disseminated cancer undergoing emergency laparotomy for perforation or obstruction, the 30-day mortality rate was 27%.¹⁷ In our study, the 30-day mortality rate for patients with disseminated malignant disease was 35%; however, based on a small population with only 15 deaths.

A strength of our study was the collection of data from electronic medical journals. In these journals, entries were made prospectively as the disease of the patient evolved and thus were not subject to recall bias. Complications were critically appraised and scored by medical professionals trained in the Clavien-Dindo classification. This would not have been possible with data from general registries based on ICD-10 and procedure codes. Even though the Clavien-Dindo classification of surgical complications is a well-established way of reporting complications, the data collection may suffer from both intra- and inter-observer variability. Complications were only registered as a score on the Clavien-Dindo, and this limits the interpretation of the results since we were not able to classify the types of complications. Our data may, therefore, be driven by one or a few types of cardiovascular complications. Due to possible masking of symptoms by postoperative analgesics and not routinely monitoring patients with troponin measurements and continuous electrocardiography postoperatively, a substantial number of cardiovascular complications may have been undetected in our cohort. Repeated measures of troponin postoperatively can be used to assess myocardial injury after surgery.¹⁸ Postoperative troponin was not routinely measured at Zealand University Hospital in the study period. Neither were any patients monitored with continuous electrocardiography postoperatively. The exact rate of cardiovascular complications after emergency laparotomy may thus be higher than reported.

Another limitation of our study was missing values in certain variables. In total, 36% of all patients were missing values for BMI, 5.5% were missing values for alcohol consumption, and 6.2% were missing values on smoking. We decided to exclude BMI from the analysis due to the high degree of missing values. Because of missing values, 227 (19%) patients were not included in the multivariate logistic

regression analysis, and our study may have been prone to a type II error due to a decrease in sample size. Unfortunately, our cohort did not contain information regarding the timing of the postoperative complications, and thus, a time-to-event analysis was not possible to conduct. Finally, the design of the current study does not allow for causal conclusions to be made.

Conclusion

In conclusion, we found no significant association between malignant disease and cardiovascular complications graded 3–5 on the Clavien-Dindo score within 30 days of emergency laparotomy. The only independent statistically significant risk factors for cardiovascular complications ranked 3–5 on the Clavien-Dindo score following emergency laparotomy were increasing age and ASA score. Cardiovascular complications are common after emergency surgery, and further research on early identification and clinical management of high-risk patients is needed.

Declarations

Ethical approval and consent to participate

Studies based on data from registers do not need approval from the Danish research bioethics committees, as study participants are never contacted, and consent is not required for the use of register information. The study's use of register data was approved by the Danish Data Protection Agency in compliance with the General Data Protection Regulation.

Consent for publication

Not applicable

Available of data and materials

This study was based on register data. The data do not belong to the authors, but to the Region of Zealand, Denmark. The authors are not permitted to share them, except in aggregate (e.g., a publication).

Competing interest

JHS and IG report grants from the Danish Cancer Society outside of the submitted work. In addition, **IG has received an unrestricted research grant from Pharmacosmos, Reponex Pharmaceuticals A/S, Perfusion Tech, Intuitive Surgical, and consultancy fees from Medtronic and Ethicon.** For the remaining authors, no conflicts were declared.

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Author Contributions

Rasmus Peuliche Vogelsang had full access to the data during the preparation of the manuscript and takes responsibility for the integrity and the accuracy of the data analysis.

RPV, JHS, MBT, JB, SE, and IG conceived and designed the study, defined in- and exclusion criteria, and outcome. JHS and JB were responsible for data extraction. JHS and RPV were responsible for data analysis and preparation of manuscript. RPV and JHS interpreted the study findings. RPV and JHS drafted the manuscript. RPV, JHS, MBT, JB, SE and IG critically reviewed the manuscript. All authors provided approval of the final version of the manuscript to be published.

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Not applicable

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Figures

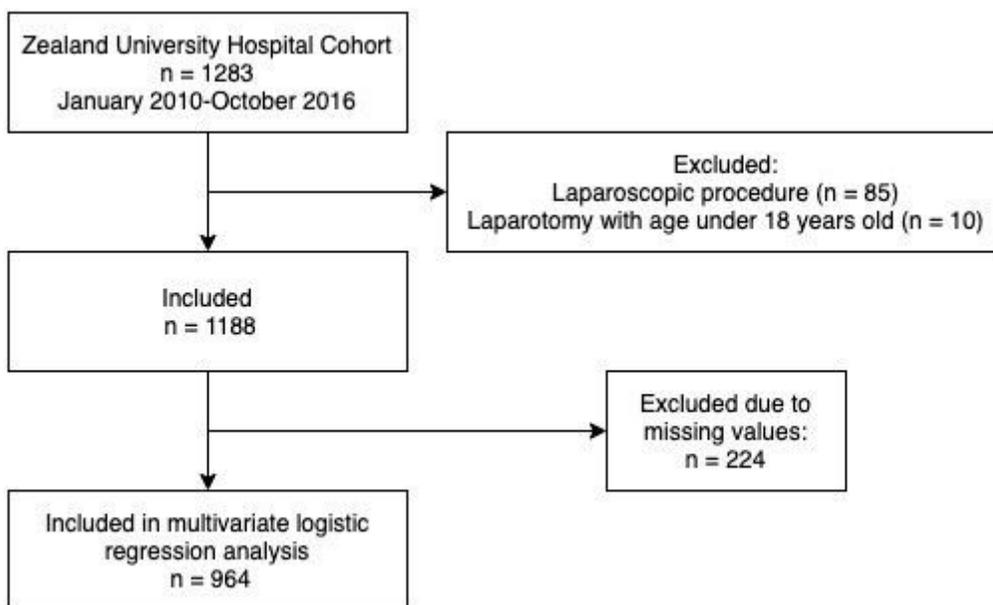


Figure 1

Flow chart of patient selection