



## Influence of Hypertension and Diabetes on Postoperative Outcomes in Cancer Patients Undergoing Moderate/High Risk Surgical Procedures

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### Abstract

**Background:** Systemic Hypertension (HTN) and Diabetes Mellitus (DM) are believed to be risk factors for adverse postoperative outcomes in patients undergoing surgical interventions, but evidence is lacking. This retrospective study evaluated the effects of HTN and DM, alone or in combination, on postoperative outcomes of elective non-cardiac surgery in cancer patients.

**Materials and Methods:** Patients (n=844) with malignancies, who underwent elective surgery at a tertiary hospital, were categorized into healthy (group A, n=339), hypertensive (group B, n=357), diabetic (group C, n=21), and hypertensive and diabetic (group D, n=127) groups. Preoperatively, all patients had systolic blood pressure  $\leq$  160 mmHg and plasma glucose level  $\leq$  140 mg/dl. Postoperative in-hospital morbidity and mortality were compared among groups.

**Results:** Postoperative complications occurred in 22 (6.5%), 21 (5.9%), 2 (9.5%), and 11 (8.7%) patients in groups A, B, C, and D, respectively (p=0.712). HTN (p=0.538), DM (p=0.990), and HTN+DM (p=0.135) did not impact the occurrence of adverse events. Patients with higher surgical risk (ASA III or IV) and those with longer surgical time had higher morbidity and mortality (p=0.001, p<0.001, respectively). In multiple logistic regression analysis, ASA status and surgical time were independent risk factors for postoperative complications (both p<0.001).

**Conclusion:** Cancer patients with preoperative comorbidities, such as HTN and DM, alone or in combination, regardless of other characteristics, do not have an increased risk of adverse postoperative outcomes.

**Keywords:** Diabetes mellitus; Hypertension; Oncologic surgery; Postoperative outcomes

### Abbreviations

ASA: American Society of Anesthesiologists; CI: Confidence Interval; DM: Diabetes Mellitus; ECG: Electrocardiogram; IBCC: Instituto Brasileiro de Controle do Câncer; OR: Odds Ratios; SPSS: Statistical Package for the Social Sciences; HTN: Systemic Hypertension

### Introduction

Investigations of the occurrence of postoperative complications requires a specialized approach, due to aspects related to both the patient's well-being and quality of life, as well as to the operational and financial management of the hospital. Although the effect of such complications on the patient is at first seen a matter of overriding importance, the impact on hospital management also requires special attention, primarily in terms of strategies that seek to reduce the incidence of such complications, and aiming to minimize the costs resulting from the increased hospitalization duration, to optimize diagnostic and therapeutic resources, and to manage beds. With this concern in mind, a "triple aim" concept for improving health care has been suggested, including improving the individual experience of care, improving the health of populations, and reducing the per capita costs of care for populations [1].

The number of non-cardiac surgeries performed around the world and the cost of these

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procedures has increased considerably in recent years. This has prompted attempts to prevent the occurrence of adverse postoperative outcomes [2]. In this context, ensuring adequate preoperative evaluation allows the institution of measures to reduce the possible risks arising from the surgical procedure, and consequently the perioperative morbidity and hospital stay [3].

Chronic diseases, such as Diabetes Mellitus (DM) and systemic arterial Hypertension (HTN), have a high prevalence in the general population and, when not adequately controlled, are reported to be related to an increased risk of postoperative complications [4-6]. This comorbidity is often associated with a decline in functional reserves and an increasing prevalence of frailty. Thus, patients with comorbidities are more likely to have suboptimal outcomes and experience more treatment-related toxicities. The impact of comorbidity is more evident in cancer patients [7]. A cohort study has demonstrated that patients with comorbidities have an increased risk of all-cause mortality after curative cancer surgery, as compared to patients without comorbidities, but analyzed only patients with esophageal cancer [8].

Although reports are limited, it has been believed that cardiovascular comorbidities can influence surgical outcomes, but no study was conducted with the primary endpoint of demonstrating the relationship between HTN or DM with postoperative outcomes in cancer patients. Such information is highly relevant for estimating the surgical risk of this population, and for optimizing pre-, peri-, and post-operative care [9,10]. However, there is a lack of evidence of the presumed association of HTN and/or DM with the occurrence of postoperative complications.

Therefore, the present study sought to elucidate the influence of HTN and DM, alone or in combination, on the in-hospital outcomes of cancer patients undergoing non-cardiac surgery that are considered to be of moderate/high risk, at a tertiary cancer center.

## Methods

### Study population

We conducted a single-centre, retrospective cohort study involving all patients who underwent elective non-cardiac surgery of moderate/high risk screened at a preoperative assessment clinic. Data were extracted from electronic clinical records.

All adult patients (age  $\geq 18$  years) of both sexes, with a secondary diagnosis of diabetes mellitus and systemic arterial hypertension, either alone or in combination, who underwent moderate to high risk non-cardiac elective surgical interventions were included in the analysis. For the purpose of this study, moderate to high risk surgery was considered to be any intracavitary procedure (skull, chest, abdomen, or pelvis) or those in which fluid replacement during surgery exceeded 30 ml/kg.

From a database of approximately 20,194 preoperative assessments, 7,500 records were analyzed sequentially, of which 844 met pre-established inclusion criteria. Patients were classified into four groups: healthy (group A,  $n=339$ ), hypertensive (group B,  $n=357$ ), diabetic (group C,  $n=21$ ), and hypertensive and diabetic (group D,  $n=127$ ). All patients had systolic blood pressure  $\leq 160$  mmHg and plasma glucose  $\leq 140$  mg/dl at the time of the preoperative clinical evaluation.

### Data collection

The variables collected from medical records included age, sex,

type of surgery, results of preoperative tests (Electrocardiogram [ECG], chest X-ray, laboratory tests [blood count, urea/creatinine, fasting glucose, and coagulogram], presence of comorbidities [DM and/or HTN], American Society of Anesthesiologists [ASA] surgical risk status), and in-hospital post-operative evolution.

An abnormal ECG was considered to be any tracing that presented a rhythm other than sinus rhythm, presence of cardiac chamber enlargement, intraventricular (right bundle branch block, left bundle branch block) or atria-ventricular block, inversion of the T wave polarity in at least two contiguous leads, more than three atrial or ventricular premature beats, or the presence of ventricular pre-excitation. Abnormal chest radiography included the presence of parenchymal infiltrates, sequela of tuberculosis, presence of pleural effusion, enlarged cardiac area, or presence of metastases. Any results other than the normative ranges of the institution's central laboratory were considered to be altered, except for blood glucose, which was considered abnormal only when values exceeded 140 mg/dl in patients with a history of DM. Surgical time was defined as the time from the moment of the incision until skin closure, excluding the anesthesia time. Adverse outcomes included any type of complication (clinical and/or surgical) that increased the length of hospital stay for each procedure performed, or death. Postoperative outcomes were studied individually and jointly as "morbimortality".

### Ethical aspects

The IBCC Oncologia Research Ethics Board in Sao Paulo, Brazil, reviewed and approved this study. Data confidentiality was maintained at all times, in accordance with Brazilian ethical regulation.

### Statistical analyses

Qualitative characteristics were summarised using absolute and relative frequency, according to adverse intra-hospital outcomes. Pearson's chi-square test was employed as appropriate. Quantitative characteristics were described according to adverse in-hospital outcomes, using summary measures (mean, standard deviation, median, minimum, and maximum) and compared using Student's *t*-tests or Mann-Whitney tests.

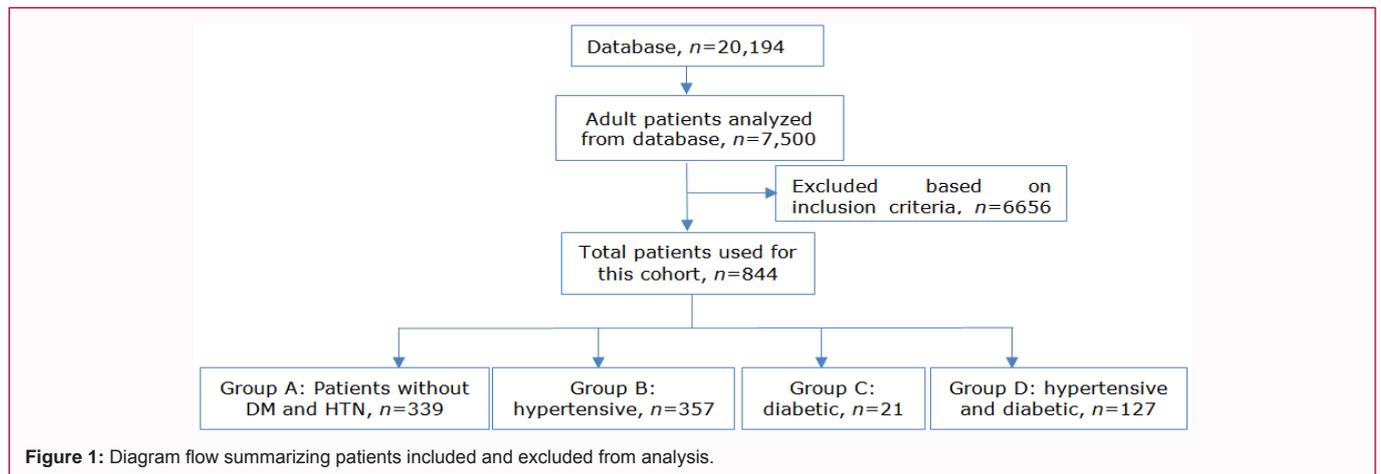
Bivariate logistic regression analyses were used to adjust for multiple predictive factors and their interactions. Odds ratios (ORs) and 95% confidence interval (95% CIs) were used to quantify the relationship between the outcomes of interest and each independent factor, while multiple logistic regression analysis was used to analyze the influence of parameters on the occurrence of adverse outcomes.

Statistical analyses were conducted in Statistical Package for the Social Sciences (SPSS) for Windows Software Version 20.0 (IBM SPSS Inc., Armonk, NY, USA). All statistical assessments were two-sided. Probability (*p*)-values below 0.05 were considered statistically significant.

## Results

The cohort included 844 patients undergoing elective surgeries. Figure 1 shows the number of patients excluded from the study at each stage of analysis.

Baseline patient characteristics are summarised in Table 1. The cohort included 116 men and 728 women. Patients in group D were significantly older than those in group A ( $p<0.001$ ) and B ( $p<0.001$ ), and those in group B were older than those in group A ( $p<0.001$ ). Patients with comorbidities had more ECG ( $p=0.002$ ), radiological ( $p<0.001$ ), and laboratory ( $p<0.001$ ) abnormalities. There were no

**Table 1:** Characteristics of the population studied in relation to the variables analyzed.

Variable	Group A		Group B		Group C		Group D		Total		P value
	n	%	n	%	n	%	n	%	n	%	
<b>Sex</b>											
Male	41	12	53	15	3	14	19	15	116	14	0.723
Female	298	88	304	85	18	86	108	85	728	86	
<b>Age (SD)</b>	46.3 ± 12.3		53.4 ± 13.4		51.8 ± 14.4		58.1 ± 13.4		51.2 ± 13.7		<0.001
<b>ECG</b>											
Normal	291	86	271	76	20	95	99	78	682	80	0.002
Altered	48	14	85	24	1	4.8	28	22	162	19	
<b>X-Ray</b>											
Normal	299	92	279	84	19	100	90	76	687	87	<0.001
Altered	25	7.7	53	16	0	0	28	24	106	13	
<b>Laboratory*</b>											
Normal	295	89	324	92	17	81	30	24	666	80	<0.001
Altered	38	11	27	7.7	4	19	97	76	166	20	
<b>ASA score</b>											
I-II	322	95	336	94	20	95	116	91	794	94	0.554
III-IV	17	5	21	5.9	1	4.8	11	8.7	50	5.9	
<b>Duration (hours)</b>											
1	86	25	96	27	10	48	25	20	217	26	0.396
2	111	33	110	31	5	24	34	27	260	31	
3	61	18	60	17	1	4.8	33	26	155	18	
4	36	11	33	9.2	3	14	13	10	85	10	
5	15	4.4	26	7.3	1	4.8	9	7.1	51	6	
6	17	5	19	5.3	0	0	7	5.5	43	5.1	
7	8	2.4	6	1.7	1	4.8	2	1.6	17	2	
8	2	0.6	5	1.4	0	0	1	0.8	8	0.9	
9	3	0.9	2	0.6	0	0	3	2.4	8	0.9	
<b>Total</b>	<b>339</b>	<b>100</b>	<b>357</b>	<b>100</b>	<b>21</b>	<b>100</b>	<b>127</b>	<b>100</b>	<b>844</b>	<b>100</b>	

\* For the purpose of this study, fasting blood glucose of up to 140 mg/dL was accepted as normal in patients with DM

ASA: American Society of Anesthesiologists; DM: Diabetes Mellitus; HTN: Systemic Hypertension; ECG: Electrocardiogram; SD: Standard Deviation

significant differences among groups in terms of ASA surgical risk (p=0.554) and the duration of surgery (p=0.396).

Adverse outcomes were observed in 22 patients in group A (6.5%), 21 (5.9%) in group B, 2 (9.5%) in group C, and 11 (8.7%) in

group D. In bivariate analysis, the presence of comorbidities in the preoperative period (HTN, DM, or HTN combined with DM) did not influence postoperative morbidity and mortality (p=0.712) (Table 2). Multivariate logistic regression analysis showed that the presence

**Table 2:** Unadjusted bivariate analysis of adverse events in relation to the variables studied.

	Morbidity and mortality				Total	p
	No		Yes			
	n	%	n	%		
<b>Comorbidity</b>						0.712 <sup>#</sup>
Patients without DM and HTN	317	93.5	22	6.5	339	
HTN	336	94.1	21	5.9	357	
DM	19	90.5	2	9.5	21	
DM + HTN	116	91.3	11	8.7	127	
<b>ECG</b>						0.254 <sup>*</sup>
Normal	640	93.8	42	6.2	682	
Altered	148	91.4	14	8.6	162	
<b>X-Ray</b>						0.075 <sup>*</sup>
Normal	647	94.2	40	5.8	687	
Altered	95	89.6	11	10.4	106	
<b>Laboratory</b>						<b>0.007<sup>*</sup></b>
Normal	629	94.4	37	5.6	666	
Altered	147	88.6	19	11.4	166	
<b>ASA score</b>						<b>0.001<sup>*</sup></b>
I	413	94.5	24	5.5	437	
II	337	94.4	20	5.6	357	
III	37	75.5	12	24.5	49	
IV	1	100	0	0	1	
<b>Duration (hours)</b>						<b>&lt;0.001<sup>#</sup></b>
1	206	94.9	11	5.1	217	
2	254	97.7	6	2.3	260	
3	145	93.5	10	6.5	155	
4	79	92.9	6	7.1	85	
5	44	86.3	7	13.7	51	
6	35	81.4	8	18.6	43	
7 or more	12	70.6	5	29.4	17	

ASA: American Society of Anesthesiologists; DM: Diabetes Mellitus; HTN: Systemic Hypertension; ECG: Electrocardiogram

\*Pearson's chi-square; #Likelihood ratio tests

of HTN (p=0.538), DM (p=0.990), and HTN combined with DM (p=0.135) did not correlate with the occurrence of adverse events in this population (Table 3).

To determine whether the presence of comorbidities has a direct influence on preoperative surgical risk (ASA status), we analyzed the effects of the presence of these comorbidities on in-hospital outcomes (morbidity and mortality), excluding the surgical risk. The presence of HTN and DM alone or in combination did not have a significant effect on adverse events when surgical risk was excluded (Table 4).

Four deaths (0.47%) were observed in the studied population. Three deaths resulted from postoperative clinical complications and one was died due to unsuccessful surgery in three sequential approaches. One death occurred in a patient from the healthy group, two in patients from the hypertensive group, and one in a patient from the hypertensive and diabetic group. There were no deaths in the diabetic group. The mortality rate was not significantly different among groups (p=0.864). Due to the small number of deaths, they are

**Table 3:** Multivariate logistic regression analysis of comorbidities as an independent variable of adverse events.

	OR	95% CI	p value
<b>Age (years)</b>	1.01	0.99–1.04	0.326
<b>X-Ray (Altered)</b>	1.74	0.79–3.82	0.169
<b>Laboratory (Altered)</b>	2.19	0.98–4.91	0.056
<b>ASA</b>	4.26	1.89–9.62	<b>&lt;0.001</b>
<b>Time of surgery</b>	1.36	1.18–1.57	<b>&lt;0.001</b>
<b>Secondary diagnosis</b>			
Patients without DM and HTN	1		
HTN	0.8	0.40–1.62	0.538
DM	1.01	0.12–8.31	0.99
DM + HTN	0.44	0.15–1.29	0.135

ASA: American Society of Anesthesiologists; DM: Diabetes Mellitus; HTN: Systemic Hypertension; CI: Confidence Interval; OR: Odds Ratio

presented together with adverse events under the name of mortality and morbidity in Table 2.

In patients with normal ECG, there were 42 adverse events, as compared to 14 adverse events among patients with at least one significant ECG change (p=0.254; Table 2). Abnormal chest radiography was noted in 13.4% patients, of which 10.4% had adverse outcomes, as compared to 5.8% of the group with normal X-ray (p=0.075). One hundred sixty six patients (19.7%) had at least one altered laboratory test, according to the pre-established criteria. Of these 11.4% had some postoperative complication, as compared to 5.6% of those who had completely normal preoperative examinations (Table 2; p=0.007).

Patients who were classified as surgical risk ASA III/IV had a higher risk of postoperative complications than those classified as ASA I/II (Table 2; p=0.001). Patients with operative time exceeding 5 hours had significantly more in hospital postoperative complications (Table 2; p<0.001). Multiple logistic regression analysis also confirmed that surgical risk and operative time (Table 3; both p<0.001) were independent predictors for postoperative adverse events.

## Discussion

This study evaluated the effects of HTN and DM, alone or in combination, on the postoperative outcomes of elective non-cardiac surgery in cancer patients. Our findings suggest that patients with preoperative comorbidities, such as HTN and DM, alone or in combination, do not have an increased risk of adverse postoperative outcomes. Rather preoperative risk (ASA status) and operative time affected the risk of postoperative adverse events.

Preoperative clinical evaluation of patients undergoing elective surgery can be performed for multiple purposes, including for detecting possible disorders that may compromise a satisfactory postoperative course [11]. Through medical history and physical examination, pre-existing or unknown diseases that may increase the risk of complications during the perioperative period can be detected. HTN and DM have a high prevalence among the population. In patients with neoplasms, the prevalence of HTN is around 40%, reaching 74% in the group aged over 65 years [6,12-15]. Similarly, in this population, DM has a prevalence of 21% [16].

It has been considered that the presence of HTN or DM alone, or both pathologies together, may increase the likelihood of

postoperative complications after non-cardiac surgery, as these are risk factors for cardiovascular disease [17-19]; however, the absence of previous evidence of the association of HTN and/or DM with the occurrence of postoperative complications prompted us to perform this investigation to clarify whether these conditions can in fact impact the postoperative course in cancer patients undergoing intermediate/high risk surgery. Regardless of the presence of comorbidities, intermediate- and high-risk surgeries have a higher intrinsic chance of involving adverse perioperative events, particularly those related to the mobilization of body fluids and the duration of the procedure. Intermediate-risk surgeries are procedures associated with adverse outcomes in 1% to 5% of cases, and high-risk surgeries are associated with complications in >5% of cases [11].

Our results indicated that patients with HTN and DM, alone or in combination, that is well-controlled pre-surgically, does not impact the postoperative outcomes of cancer patients undergoing non-cardiac intermediate/high-risk surgical interventions, as compared to patients without DM or HTN. A recent study that evaluated 203 patients in a mixed population (with and without cancer) [20], but with risk factors for cardiovascular complications, who underwent major non-cardiac thoracic surgery also found no association between the presence of HTN or DM with adverse outcomes in the postoperative period.

Abnormalities on chest radiography and ECG were not associated with an increase in morbidity and mortality in our study, corroborating findings by previous studies that showed that requesting these preoperative tests for asymptomatic patients offers little or no benefit [21-23]. In elderly individuals, chest X-ray may be abnormal, but without necessarily increasing the surgical risk [21]. There are also doubts in the literature regarding the benefit of using ECG in the preoperative period in asymptomatic patients, considering that the incidence of abnormal results increases with age and may not be related to increased adverse outcomes [22,23].

In the composition of surgical risk, the presence of comorbidities is relevant. In our study, preoperative risk assessment was categorized into ASA I/II and ASA III/IV risk status. We noted that the presence of a higher surgical risk was an independent predictor of postoperative complications, which has been established previously. This indicates that we had suitably adjusted for confounding factors. In addition, we performed multivariate logistic regression analysis with and without including this surgical risk variable; the presence of these comorbidities did not correlate with an increase in the number of adverse events, irrespective of inclusion of ASA status.

Most procedures (70%) had an operative time <3 h; patients with a prolonged surgical time (>5 h) had significantly more adverse outcomes, as corroborated by previous studies [24,25]. Early recognition and intervention for any perioperative complications may help these patients and also reduce health care costs.

Our study had some limitations that were mainly inherent to the retrospective analysis of administrative databases. The study was conducted retrospectively at a single centre, which might limit the generalization of its results. Additional limitations include that the vast majority of procedures had an effective duration of surgery of no more than 3 h, and knowing that the surgical time is a predictor of postoperative complications, it is not clear whether these comorbidities would become significant in longer surgeries. In addition, most patients in this study were female. Given the scarcity

of studies seeking to correlate the characteristics inherent to patients in the preoperative period with the outcomes in the postoperative period, further research is needed improve understanding of the impact of these comorbidities in different populations of individuals submitted to more diverse surgical procedures.

In summary, with the use of a representative database, we found that, in a population of cancer patients undergoing elective moderate/high risk surgeries, a previous diagnosis of HTN and DM, alone or combined (properly controlled), did not correlate with an increase in in-hospital morbidity and mortality.

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