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Impact of Pulmonary Hypertension on the Outcomes of Noncardiac Surgery

Predictors of Perioperative Morbidity and Mortality

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OBJECTIVES We sought to determine the predictors of short-term morbidity and mortality (<30 days) after noncardiac surgery in patients with pulmonary hypertension (PH).

BACKGROUND Pulmonary hypertension is considered to be a significant preoperative risk factor.

METHODS The PH and surgical data bases were matched from 1991 to 2003. Patients were excluded if PH was secondary to left heart disease, not present before surgery, or the procedure involved cardiopulmonary bypass. Univariate and multivariate logistic regression analyses were used to identify variables associated with short-term morbidity and mortality.

RESULTS Of 1,276 patients in the PH database, 145 patients (73% female) met all study criteria. The mean age (±SD) was 60.1 ± 16.0 years. Right ventricular systolic pressure (RVSP) (mean ± SD) on the two-dimensional echocardiogram was 68 ± 21 mm Hg. There were 60 patients (42%) who experienced one or more short-term morbid event(s) (1.8 events/patient experiencing any event). A history of pulmonary embolism ($p = 0.01$), New York Heart Association functional class ≥II ($p = 0.02$), intermediate- to high-risk surgery ($p = 0.04$), and duration of anesthesia >3 h ($p = 0.04$) were independent predictors of short-term morbidity. There were 10 early deaths (7%). A history of pulmonary embolism ($p = 0.04$), right-axis deviation ($p = 0.02$), right ventricular (RV) hypertrophy ($p = 0.04$), RV index of myocardial performance ≥0.75 ($p = 0.03$), RVSP/systolic blood pressure ≥0.66 ($p = 0.01$), intraoperative use of vasopressors ($p < 0.01$), and anesthesia when nitrous oxide was not used ($p < 0.01$) were each associated with postoperative mortality.

CONCLUSIONS In patients with PH undergoing noncardiac surgery with general anesthesia, specific clinical, diagnostic, and intraoperative factors may predict worse outcomes. (J Am Coll Cardiol 2005;45:1691–9) © 2005 by the American College of Cardiology Foundation

Surgery poses a significant risk for patients with pulmonary hypertension (PH) (1,2). Right ventricular (RV) failure, persistent postoperative hypoxia, and coronary ischemia are among the potential perioperative complications (1,3). Preoperative mean pulmonary artery pressure (MPAP) >30 mm Hg has been shown to be a significant independent predictor of postoperative mortality in over 2,000 patients undergoing cardiopulmonary bypass (2). Increased perioperative morbidity and mortality of adult patients with PH have been described previously in case reports, small series, and retrospective analyses of surgical data bases (1–10). However, most of these reports have focused on cardiopulmonary surgeries, often with cardiopulmonary bypass. Such operations, independent of the presence of PH, carry an elevated risk of morbidity and mortality compared with many noncardiac operations (11–13).

The primary aim of this study was to evaluate the incidence of perioperative (≤30 days) morbidity and mortality in adult patients with PH undergoing noncardiac surgery with general anesthesia at a large tertiary care medical center. We investigated multiple baseline demographic characteristics, clinical parameters, and intraoperative interventions to determine the specific variables that may be associated with the occurrence of short-term postoperative complications. Secondary analyses focused on identification of parameters that were associated with an increased length of hospital stay (LOS) after surgery.

METHODS

Study population. The study protocol was approved by the Mayo Foundation Institutional Review Board. The PH electronic data base was cross-referenced with the data base of all patients who had undergone monitored anesthesia care, deep sedation/analgesia, or general anesthesia from July 1991 to December 2003 at our medical center. All patients with resting two-dimensional Doppler echocardiographic (2D echo) right ventricular systolic pressure (RVSP) ≥35 mm Hg were included in the study. Patients were excluded if age at the time of surgery was <18 years, etiology for PH was considered left heart disease, consent to research authorization was not given (as mandated in Minnesota Statute 144.335), PH was not clinically diag-

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Abbreviations and Acronyms

2D echo	= two-dimensional Doppler echocardiogram
IQR	= interquartile range
LOS	= length of hospital stay
MPAP	= mean pulmonary artery pressure
6MWT	= six-minute walk test
NYHA	= New York Heart Association
PH	= pulmonary hypertension
RV	= right ventricular
RVIMP	= right ventricular index of myocardial performance
RVSP	= right ventricular systolic pressure
SBP	= systolic blood pressure

nosed before surgery, or the procedure involved neuraxial or other regional anesthesia, monitored anesthesia care, cardiac surgery, or any other surgery requiring cardiopulmonary bypass.

Analysis of preoperative factors. One of the authors (G.R.) reviewed the medical records of all eligible patients and extracted demographic, clinical, and diagnostic data (Table 1). Right heart catheterization and 2D echo data were included if performed within three years of the index surgical date. The 2D echo performed closest to the surgical date was used if there were multiple 2D echo scans performed. The standard 6-min walk test (6MWT) was included if performed within two years of the index surgical date. Major comorbid conditions were defined according to Hosking et al. (14) and have been referenced in epidemiologic studies from our institution's Department of Anesthesiology. The major comorbidities identified were cardiovascular disease (pharmacologically treated systemic hypertension, coronary artery disease, history of or current atrial fibrillation, history of deep venous thrombosis, or history of cerebrovascular disease [stroke, transient ischemic attack, or previous carotid endarterectomy]), pulmonary disease (chronic thromboembolic pulmonary disease or obstructive or restrictive pulmonary disease), hepatic disease (hepatitis, cirrhosis, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension, or aspartate aminotransferase >45 U/l), renal disease (creatinine >2 mg/dl or use of dialysis), connective tissue disease (systemic lupus erythematosus, scleroderma, or mixed connective tissue disease), hematologic malignancy (leukemia, lymphoma, myelodysplastic syndrome, or hyperviscosity syndrome), and pharmacologically treated diabetes mellitus.

As part of the standard 2D echo examination, the presence of RV hypertrophy was determined by assessing the RV wall thickness from multiple views. The right ventricular index of myocardial performance (RVIMP), also known as the RV Doppler Tei index, was calculated by dividing the sum of RV isovolumic relaxation and contraction times by the ejection time interval (15–18) and was categorized as abnormal if ≥0.75. Hemodynamic studies have used the ratio of pulmonary vascular resistance to systemic vascular resistance (0.50 to 0.74 [moderate PH] and ≥0.75 [severe PH]) to account for the influence of systemic hypertension on pulmonary artery pressure (19,20). In our study, PH was considered at least moderate if the ratio of right ventricular systolic pressure (RVSP) to concurrent systemic systolic blood pressure (SBP) was <0.66 and severe if ≥0.66. The left atrial volume index was calculated as the product of left atrial areas obtained in the apical two-chamber and four-chamber views times the lesser of the length obtained in the apical two-chamber and four-chamber views × 0.85 divided by the body surface area (21). Pulmonary function tests were classified as normal or abnormal (obstructive, restrictive, or mixed pattern). In accordance with standard protocol (22), the 6MWT was performed in a level corridor, and patients were instructed to walk at their own pace.

Intraoperative factors. Data extracted from the operative record included duration of anesthesia (referenced to start and end time of general anesthetic), inhalation anesthetic used, and intraoperative administration of beta-adrenergic blockers and major vasopressor agents (i.e., dopamine, epinephrine). The type of surgery was categorized as low risk (breast, dermatologic, ear, nose, and throat/oral, gynecologic, neurologic, plastic/reconstructive, and urologic) or intermediate to high risk (gastrointestinal/major abdominal, orthopedic, thoracic, vascular, and transplant [liver, kidney, pancreas]).

Outcome measures. The occurrence of perioperative outcome events was determined from the review of hospital progress notes, postanesthesia care unit records, discharge summary note, and follow-up outpatient notes. For this analysis, we considered morbid events and fatal events as "early" if they occurred intraoperatively or were ≤30 days from the date of surgery. The LOS was determined from the date of noncardiac surgery to dismissal date (or date of in-hospital death) of the patient.

Definition of morbidity. We specifically defined morbidity as the occurrence of any of the following: 1) congestive heart failure: new pulmonary edema, elevated jugular venous distension >10 mm Hg, or lower extremity edema and use of diuretic or afterload- and/or preload-reducing medications, or physician documentation that the patient developed congestive heart failure; 2) cardiac ischemic events (electrocardiographic ST-segment elevation or depression of ≥1 mm or elevated or inverted T waves) with or without myocardial infarction (appearance of new Q waves ≥0.04 s wide and 1 mV in depth accompanied by troponin T elevation ≥0.03 ng/ml or elevation in creatine kinase-MB fraction [>100 IU/l and MB band >5%]; 3) stroke; 4) respiratory failure: prolonged intubation >24 h or reintubation, tracheostomy placement, or pneumonia/hypoxia necessitating postoperative oxygen therapy in patients who did not require it preoperatively; 5) hepatic dysfunction: aspartate aminotransferase >45 U/l in a patient with normal preoperative aspartate aminotransferase or >50% elevation compared with baseline; 6) renal insufficiency: increase in creatinine to >2 mg/dl in a patient with normal preopera-

Table 1. Baseline Characteristics of Patients With Pulmonary Hypertension Undergoing Noncardiac Surgery (n = 145)

Characteristic		n (%)
Female		106 (73)
Pulmonary hypertension*		
Pulmonary arterial hypertension		
Idiopathic		29 (20)
Associated with		
Collagen vascular		18 (12)
Portal hypertension		14 (10)
Congenital systemic to pulmonary shunts		10 (7)
Other		8 (6)
PH associated with lung diseases and/or hypoxemia		
Lung disease: COPD, interstitial, restrictive		20 (14)
Obstructive sleep apnea		7 (5)
PH due to chronic thrombotic and/or embolic disease		12 (8)
Nonspecific		27 (19)
New York Heart Association functional class		
I		39 (27)
II		67 (46)
III/IV		39 (27)
Smoking status		
Never smoker		80 (55)
Ex-smoker (quit >6 months)		55 (38)
Current smoker		10 (7)
Preoperative comorbidity		
Pulmonary		
COPD		38 (26)
Obstructive sleep apnea		23 (16)
Restrictive lung disease		16 (11)
History of pulmonary thromboembolism		12 (8)
Cardiovascular		
Systemic hypertension		72 (50)
Coronary artery disease		25 (17)
Previous CABG		14 (10)
Previous PCI		10 (7)
History of or current atrial fibrillation		25 (17)
History of deep venous thrombosis		15 (10)
History of cerebrovascular disease		12 (8)
Other		
Liver disease		25 (17)
Renal disease		25 (17)
Connective tissue disease		23 (16)
Diabetes mellitus		18 (12)
Hematologic malignancy		12 (8)
Outpatient medication use		
Diuretic		79 (54)
Beta-adrenergic blockers		43 (30)
ACE-I/ARB		40 (28)
Calcium channel blocker		40 (28)
Warfarin sodium		41 (28)
Digoxin		25 (17)
Steroid		21 (14)
Epoprostenol		15 (10)
Bosentan		6 (4)
Diagnostic and hemodynamic data	n†	Mean ± SD
6-min walk distance (m)	55	319 ± 111
2D echo RVSP (mm Hg)	145	68 ± 21
Catheterization-derived RVSP (mm Hg)	68	68 ± 22
Catheterization-derived MPAP (mm Hg)	66	44 ± 15
Catheterization-derived wedge pressure (mm Hg)	65	15 ± 8

*Classification modified from Venice 2003 Revised Clinical Classification of PH (23). Patients were categorized as "nonspecific" if multiple co-exisiting factors contributed to PH or if PH was present in the setting of comorbidities that did not permit a confident diagnosis of idiopathic pulmonary arterial hypertension. †Values may be <145, because data variables were not available for all patients.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; MPAP = mean pulmonary artery pressure; PCI = percutaneous coronary intervention; PH = pulmonary hypertension; RVSP = right ventricular systolic pressure.

tive creatinine or >50% elevation compared with baseline and/or initiation of hemodialysis; 7) sepsis or hemodynamic instability necessitating inotropic/vasopressor support; and 8) cardiac dysrhythmia: new-onset atrial fibrillation, supraventricular tachycardia, bradycardia with conduction block, or ventricular tachycardia/fibrillation.

Defining the cause of mortality. Major causes of death were derived from autopsy and/or clinician reports; patients could have one or more cause(s) of death. Congestive heart failure, myocardial infarction, respiratory failure, liver/renal dysfunction, stroke, and sepsis/hemodynamic instability were coded as previously defined.

Statistical analyses. Data are summarized with count and percentage data for nominal or dichotomous variables and mean ± SD or median and interquartile range (IQR) (25th to 75th percentile) for continuous variables. Clinical variables potentially predictive of short-term morbidity and mortality were first identified by logistic regression analysis, which assessed the association of each characteristic with the respective outcome. Multivariate logistic regression analysis was modeled using a stepwise variable selection procedure to identify variables with the strongest independent association with morbidity. Variables deemed clinically relevant and all variables with $p \leq 0.20$ in the univariate model were considered for inclusion in the multivariate logistic regression model.

For each characteristic, the median LOS and IQR were reported. The LOS displayed a markedly right-skewed, nonparametric distribution, and thus log LOS was used as the dependent variable. Univariate linear regression analysis was used to assess the association of each characteristic with log LOS. Multivariate linear regression analysis was performed with respect to log LOS using the stepwise variable selection procedure, as performed for the morbidity model.

We used JMP 5.1 statistical software (2003 SAS Institute, Inc., Cary, North Carolina) for all analyses. For both univariate and multivariate analyses, $p < 0.05$ was necessary for retention of variables in the given model.

Table 2. Incidence and Type of Early (≤30 Days) Morbidity in Patients With Pulmonary Hypertension (n = 145) After Noncardiac Surgery

Morbidity	Patients* (n)	Frequency (%)
Respiratory failure	41	28
Cardiac dysrhythmia	17	12
Congestive heart failure	16	11
Renal insufficiency	10	7
Sepsis/hemodynamic instability	10	7
Hepatic dysfunction	6	4
Ischemia/myocardial infarction	5	4
Stroke	1	1

*Patients may have had one or more morbid event(s).

RESULTS

Preoperative characteristics. Of 1,276 patients in the PH database, 21 denied research authorization (1.6%) and were excluded. Of the remaining 1,255 patients, 349 (28%) had undergone anesthetic procedures. Patients who had undergone cardiovascular or pulmonary surgery requiring cardiopulmonary bypass as their only recorded surgery (n = 65), patients who had no clinical diagnosis of PH at the time of surgery (n = 69), patients with PH secondary to left heart disease (n = 19), and patients who underwent neuraxial/other regional anesthesia or monitored anesthesia care (n = 51) were excluded.

The final study population comprised 145 adult patients with PH who had noncardiac surgery with general anesthesia from July 1991 to December 2003. Baseline clinical characteristics (including PH classification according to the Venice 2003 guidelines) (23), preoperative outpatient medication use, and baseline hemodynamic data of the study population are provided in Table 1. The mean (±SD) age was 60.1 ± 16.0 years. The RVSP (mean ± SD) on 2D echo was 68 ± 21 mm Hg. The MPAP in the 66 patients who underwent right heart catheterization was 44 ± 15 mm Hg.

Short-term morbidity. Of 144 patients who survived surgery, 60 (42%) had one or more short-term morbid event(s) (1.8 events/patient experiencing any event). The most frequent postoperative morbid events noted were respiratory failure (28%), cardiac dysrhythmia (12%), and congestive heart failure (11%) (Table 2).

Univariate predictors of short-term morbidity. Patient preoperative clinical characteristics that were associated with increased short-term morbidity were New York Heart Association (NYHA) functional class ≥II, history of pulmonary embolism, and presence of obstructive sleep apnea (Table 3). Patients who underwent intermediate- to high-risk surgery were 2.5 times more likely to experience a morbid event as compared with patients who had low-risk surgery (Table 4). Similarly, patients who underwent >3 h of anesthesia or received intraoperative vasopressor support with dopamine or epinephrine were also significantly more likely to suffer short-term morbidity. None of the selected parameters derived from the 6MWT, electrocardiogram, or 2D echo were predictive of morbidity (Table 5).

Multivariate predictors of short-term morbidity. A history of pulmonary embolism, NYHA functional class ≥II, intermediate- to high-risk surgery, and duration of anesthesia >3 h were independent predictors of postoperative short-term morbidity in the multivariate model (Table 6).

Univariate predictors of early (≤30 days) postoperative mortality. Of 145 surgical procedures, there were 10 early deaths (7%), one of which occurred during the operation as a complication of RV failure. Respiratory failure (60%) and RV failure (50%) were the most frequent contributing causes of death (patients could have one or more cause[s] of death). The limited number of early deaths precluded robust multivariate analysis to identify independent predictors of early mortality, and thus, only the univariate analyses are presented.

Right-axis deviation on the electrocardiogram ($p = 0.02$), RV hypertrophy ($p = 0.04$), RVIMP ≥0.75 ($p = 0.03$), and RVSP/SBP ≥0.66 ($p = 0.01$) by 2D echo were all significantly associated with early mortality. A history of pulmonary embolism ($p = 0.04$), anesthesia when nitrous oxide was not used ($p < 0.01$), and intraoperative use of dopamine ($p < 0.01$) and epinephrine ($p < 0.01$) were also associated with early mortality on univariate analysis.

Length of hospital stay. The median (25th, 75th percentile) LOS for all patients was 5 (2, 7) days. NYHA functional class ≥II, history of systemic hypertension, intermediate- to high-risk surgery, duration of anesthesia >3 h, and intraoperative vasopressor use were each significantly associated with an increased LOS (Tables 3 to 5). There was a trend toward increased LOS in patients who received intraoperative acute beta-adrenergic blockade ($p = 0.09$). Patients who were administered anesthesia without nitrous oxide and those who performed <330 m on the 6MWT were significantly more likely to have an increased LOS. Patients with any morbidity also had a significantly greater median LOS (7 days, IQR 4, 15), as compared with patients without morbidity (3 days, IQR 1, 5.5) ($p < 0.01$).

In the multivariate linear regression analysis, systemic hypertension, duration of anesthesia >3 h, intraoperative dopamine use, and intermediate- to high-risk surgery were each independent predictors of increased LOS (Table 7).

DISCUSSION

This study has demonstrated that several preoperative patient characteristics and results from diagnostic tests, as well as intraoperative factors, are independent predictors of short-term perioperative (≤30 days) morbidity and mortality in adult patients with PH undergoing noncardiac surgery under general anesthesia. Information on the perioperative morbidity and mortality of patients with PH who undergo noncardiac surgery is scarce. In our study, almost half of the 145 patients studied (n = 60 [42%]) experienced at least one short-term morbid event and 10 patients had early death (7%).

Table 3. Univariate Association of Patient Demographics and Comorbidities With Perioperative Morbidity and Length of Hospital Stay* (Days) After Noncardiac Surgery

Characteristic	Patients n (%)†	Morbidity n (%)	p Value	LOS (Days) Median (IQR)	p Value‡
Age (yrs)			0.84		0.11
≤50	35 (24)	15 (43)		2 (2–7)	
>50	110 (76)	45 (41)		5 (2–7)	
Gender			0.14		0.25
Male	39 (27)	20 (51)		5 (3–8)	
Female	106 (73)	40 (38)		4.5 (2–7)	
Type of pulmonary hypertension			0.82		0.49
PAH	79 (55)	32 (41)		4 (2–8)	
Other PH	66 (45)	28 (42)		5 (2–7)	
New York Heart Association functional class			<0.01§		<0.01
I	39 (27)	9 (23)		3 (1–5)	
II/III/IV	106 (73)	51 (48)		5.5 (2–7.25)	
Coronary artery disease			0.29		0.49
No	120 (83)	52 (43)		5 (2–7)	
Yes	25 (17)	8 (32)		4 (2–6.5)	
Diabetes mellitus			0.20		0.70
No	127 (88)	50 (39)		4 (2–7)	
Yes	18 (12)	10 (56)		5 (4–6.25)	
Systemic hypertension			0.28		<0.01
No	73 (50)	27 (37)		3 (2–7)	
Yes	72 (50)	33 (46)		6 (3–8.75)	
Pulmonary function			0.92		0.64
Normal	22 (20)	10 (45)		3.5 (1.75–7)	
Abnormal	88 (80)	39 (44)		5 (2–7)	
History of pulmonary embolism			0.01		0.55
No	133 (92)	51 (38)		5 (2–7)	
Yes	12 (8)	9 (75)		6.5 (2.25–13.5)	
History of deep venous thrombosis			0.13		0.25
No	130 (90)	51 (39)		5 (2–7)	
Yes	15 (10)	9 (60)		6 (3–20)	
Obstructive sleep apnea			0.04		0.37
No	122 (84)	46 (38)		4.5 (2–7)	
Yes	23 (16)	14 (61)		5 (3–7)	
Creatinine (mg/dl)			0.46		0.68
≤2.0	129 (89)	52 (40)		5 (2–7)	
>2.0	16 (11)	8 (50)		5 (2.25–7.75)	

*From surgery to hospital discharge. †Values may be <145, because data variables were not available for all patients. ‡p values were calculated using log LOS as the dependent variable. §p = 0.02 by the chi-square test for trends with incremental New York Heart Association functional class.

IQR = interquartile range (25th to 75th percentile); LOS = length of hospital stay; PAH = pulmonary arterial hypertension, as defined per Venice 2003 guidelines (23) and as noted in Table 1; PH = pulmonary hypertension.

Incidence of perioperative morbidity and mortality. Our study demonstrated a 7% perioperative mortality rate, indicating the serious impact of PH. There are no published data to provide a direct comparison with our study, as the majority of reports have focused on patients with PH who have undergone cardiopulmonary bypass (1,5,7,24–29). In patients with PH undergoing pulmonary thromboendarterectomy, mortality rates have ranged from 4.4% to as high as 24% (28–31). In a retrospective study of 2,066 patients who underwent cardiopulmonary bypass, PH was the only baseline factor independently predictive of perioperative mortality (odds ratio 2.1) (2). Others reported a ≤30-day perioperative mortality rate of 5.0% in 59 patients with severe PH who underwent mitral valve surgery (32). This is comparable to the 7% perioperative mortality rate found in the present study.

A few studies have examined the outcomes of patients with PH undergoing noncardiac surgery (33,34). However, these series have described PH patients who have an additional high-risk clinical condition, and this makes a direct comparison to our study population problematic. Pregnant patients with PH and Eisenmenger's syndrome undergoing caesarean section have a maternal mortality up to 70% (33). Krowka et al. (34) reported a 35% mortality rate in patients with PH who underwent orthotopic liver transplantation; 93% of the deaths were secondary to cardiopulmonary compromise and 10 of the 14 deaths occurred during the course of hospitalization. In our study, the type of surgery was significantly associated with increased morbidity, as opposed to mortality. More than half (61.5%) of the patients who underwent thoracic and 48% of patients undergoing orthopedic surgery experienced morbidity, as opposed to 16.7% of patients who underwent either gynecologic/urologic or plastic/dermatologic/breast surgery.

Because there is limited information in the literature

Table 4. Univariate Association of Operative Characteristics With Perioperative Morbidity and Length of Hospital Stay* (Days) After Noncardiac Surgery

Characteristic	Patients n (%)†	Morbidity n (%)	p Value	LOS Median (IQR)	p Value‡
Type of surgery			<0.01		<0.01
Low risk	31 (21)	6 (19)		2 (0, 4)	
Intermediate/high risk	114 (79)	54 (47)		6 (3, 8)	
Duration of anesthesia			0.02§		<0.01
≤3 h	94 (65)	32 (34)		3 (1, 6)	
>3 h	50 (34)	27 (54)		7 (4, 15)	
Intraoperative nitrous oxide			0.09		0.04
No	66 (46)	32 (49)		6 (2, 8.25)	
Yes	78 (54)	27 (35)		4 (2, 6.25)	
Intraoperative acute beta-blockade			0.18		0.09
No	126 (88)	49 (39)		4.5 (2, 7)	
Yes	18 (13)	10 (56)		7 (3.75, 12)	
Intraoperative dopamine			<0.01		<0.01
No	132 (92)	48 (36)		4 (2, 7)	
Yes	12 (8)	11 (92)		12 (7, 21)	
Intraoperative epinephrine			<0.01		0.03
No	133 (92)	49 (37)		4 (2, 7)	
Yes	11 (8)	10 (91)		9 (6, 16)	

*From surgery to discharge. †Values may be <145, because data variables were not available for all patients. ‡p values calculated using log LOS as the dependent variable. §p < 0.01, duration of anesthesia analyzed as a continuous variable.
Abbreviations as in Table 3.

Table 5. Univariate Association of Hemodynamic and Cardiac Performance Characteristics With Perioperative Morbidity and Length of Hospital Stay* (Days) After Noncardiac Surgery

	Patients n (%)†	Morbidity n (%)	p Value	LOS (Days) Median (IQR)	p Value‡
Echocardiogram					
Ejection fraction			0.08		0.41
<0.50	9 (6)	1 (11)		3 (1.5–5.5)	
≥0.50	136 (94)	59 (43)		5 (2–7)	
Right ventricular hypertrophy			0.67		0.68
No	61 (42)	24 (39)		5 (2–7)	
Yes	84 (58)	36 (43)		4.5 (2–7)	
RVIMP			0.36		0.34
<0.75	106 (90)	45 (42)		5 (2–7)	
≥0.75	12 (10)	3 (25)		3.5 (1–6.75)	
RVSP/SBP ratio			0.22§		0.85
<0.66	110 (76)	42 (38)		5 (2–7)	
≥0.66	34 (24)	17 (50)		3 (2–7.25)	
Left atrial volume index (ml/m^2)			0.13		0.33
≤27	33 (26)	17 (52)		3 (1.5–7)	
>27	96 (74)	35 (36)		5 (2–7)	
Electrocardiogram					
Right atrial enlargement			0.21		0.37
No	131 (90)	52 (40)		5 (2–7)	
Yes	14 (10)	8 (57)		5 (2–9.25)	
Right ventricular hypertrophy			0.32		0.41
No	130 (90)	52 (40)		5 (2–7)	
Yes	15 (10)	8 (53)		2 (1–8)	
Right-axis deviation			0.59		0.77
No	119 (82)	48 (40)		5 (2–7)	
Yes	26 (18)	12 (46)		3 (2–7.25)	
6-min walk test					
Distance (m)			0.47		0.03
≥330	27 (49)	9 (33)		3 (2–5)	
<330	28 (51)	12 (43)		5.5 (2.25–7.75)	

*From surgery to discharge. †Values may be <145, because data variables were not available for all patients. ‡p values calculated using log LOS as the dependent variable. §p = 0.14, RVSP/SBP analyzed as a continuous variable.
RVIMP = right ventricular index of myocardial performance; RVSP/SBP = right ventricular systolic pressure/systolic blood pressure; other abbreviations as in Table 3.

Table 6. Variables Considered Independent Predictors in a Multivariate Logistic Regression Model of Short-Term Morbidity After Noncardiac Surgery

Characteristic	p Value	OR (95% CI)
History of pulmonary embolism	0.01	7.3 (1.9–38.3)
New York Heart Association functional class ≥II	0.02	2.9 (1.2–7.7)
Intermediate/high-risk surgery	0.04	3.0 (1.1–9.4)
Duration of anesthesia >3 h	0.04	2.9 (1.03–4.6)

CI = confidence interval; OR = odds ratio.

describing the perioperative morbidity and mortality of patients with PH undergoing noncardiac surgery, it is of interest to compare our findings to other "high-risk" patient populations undergoing noncardiac surgery. In 367 elderly patients (age ≥80 years) undergoing noncardiac surgery, 25% experienced adverse postoperative complications (cardiac, pulmonary, and neurologic) and 4.6% died during their hospitalization (35). Similarly, in 177 elderly patients (≥65 years old) who underwent noncardiac surgery, 22% experienced cardiac or pulmonary complications and 3.4% died during their hospitalization (36). In contrast, our study population had a higher perioperative cardiopulmonary complication (38%) and mortality rate (7%), as compared with the "high-risk" patient populations as described (35,36).

Predictors of perioperative morbidity and mortality. Right ventricular failure was a contributing cause of death in 50% of patients. In addition to a history of pulmonary embolism, perioperative mortality was associated with preoperative electrocardiographic findings, abnormal 2D echo parameters, and intraoperative vasopressor use. In our study, the preoperative RVSP to SBP ratio was significantly associated with short-term mortality. This is consistent with Krowka's study, in which all patients with MPAP ≥50 mm Hg died, whereas patients with MPAP <35 mm Hg survived (34). Miyamoto et al. (22) demonstrated that the 6MWT was predictive of mortality in 43 patients with primary PH. In contrast, the 6MWT in our study was not associated with early mortality, and it is possible that the 6MWT may be more predictive of long-term outcome. In a high-risk nonsurgical population of 81 patients with severe primary PH, the right atrial index was a univariate predictor of mortality (37). Our study patients had varying severity and different types of PH; this may explain why right atrial enlargement on the electrocardiogram trended toward but did not reach statistical significance with respect to short-term mortality ($p = 0.06$). In a study of 53 patients with primary PH, the RV Doppler Tei index was independently predictive of cardiac death and lung transplantation (38). This is consistent with our findings, as RVIMP ≥0.75 was associated with perioperative mortality.

Table 7. Variables Considered Independent Predictors in a Multivariate Linear Regression Model of Length of Hospital Stay After Noncardiac Surgery*

Characteristic	p Value	Estimate† (95% CI)
Systemic hypertension	<0.01	1.4 (1.1–1.8)
Duration of anesthesia >3 h	<0.01	1.5 (1.1–1.9)
Intraoperative dopamine use	<0.01	1.9 (1.2–2.9)
Intermediate/high-risk surgery	<0.01	2.0 (1.5–2.6)

*Log length of hospital stay (LOS, days, from surgery to discharge) used as the response given nonparametric distribution of LOS. †Estimate is the additional LOS incurred in the presence, compared with the absence, of the characteristic.
CI = confidence interval.

Respiratory failure was the most frequent perioperative morbidity encountered in our study (28% of patients). In a case series, among six patients who underwent orthotopic liver transplantation for severe hepatopulmonary syndrome, the two patients with preexisting PH were oxygen dependent for a longer period of time (39). Other isolated cases also suggest that PH may be a major risk factor for prolonged ventilatory support after cardiac surgery (25).

Intraoperative dopamine and epinephrine use were associated with increased short-term morbidity and mortality in our study population. Use of these agents likely reflects intraoperative complications (i.e., hypotension) and the need for hemodynamic stabilization. Thus, vasopressor use may be more a sign rather than a predictor of increased short-term morbidity. Although theirs was not specifically a PH population, Liu and Leung (35) demonstrated that intraoperative use of vasopressor agents was associated with increased in-hospital morbidity and mortality after noncardiac surgery in a geriatric population.

Length of stay. Baseline functional status (NYHA functional class and 6MWT), history of systemic hypertension, numerous intraoperative factors, as well as the occurrence of any morbid event, were strongly associated with LOS (Tables 3 to 5). In the general geriatric population (35), any intraoperative vasopressor use, as well as any morbid event, was highly associated with LOS. In our multivariate model, dopamine use persisted as an independent predictor of LOS. Although Liu and Leung (35) did not specify preoperative NYHA functional class, a history of congestive heart failure was significantly associated with increased LOS in that study. However, parameters associated with baseline functional status (NYHA functional class and 6MWT) did not retain significance in our multivariate model.

Study limitations. There are limitations inherent to the retrospective nature of this study. Both known and unknown confounding variables may not have been evenly distributed among patients and thus not accounted for in the analyses. Although we have identified several variables associated with morbidity, mortality, and LOS in patients with PH, we cannot conclude causality. The identified variables may be surrogate markers of other unidentified clinical or diagnostic characteristics. Although hospital and outpatient records were thoroughly reviewed for outcome events, some patients may not have sought medical care for complications arising after hospital discharge or may have sought medical care at a different institution. Thus, the morbidity, mortality, and LOS analyses for PH patients undergoing noncardiac surgery may be underestimates. In addition, almost 75% of patients were in NYHA functional class I or II, and only 13% of patients were taking a prostanoid or endothelin antagonist. The applicability of the results of this study to other populations of patients with PH is thus limited.

We also considered patients eligible for the study based on 2D echo RVSP ≥35 mm Hg. This deviates from the 1998 World Health Organization criteria for PH, in which MPAP ≥25 mm Hg at rest or ≥30 mm Hg with exercise is considered diagnostic (40,41), but less than half of the study population (46%) had catheterization-derived MPAP. Nonetheless, we believe the diagnosis of pulmonary hypertension by 2D echo is a reality in daily practice. Several published articles have demonstrated the usefulness, reliability, and accuracy of noninvasive parameters derived by 2D Doppler echo in comparison with those obtained by cardiac catheterization (42–44).

It is also possible that we did not have enough power to detect smaller but statistically significant associations or correlations between certain characteristics and outcome measures. The limited sample size is especially pertinent to the limited number of early deaths (n = 10), which precluded any meaningful multivariate analysis. A larger study of adult patients with PH may therefore be warranted.

Conclusions. This study suggests that patients with PH undergoing noncardiac surgery with general anesthesia carry an elevated risk of perioperative morbidity and mortality. Variables in clinical history and intraoperative factors were predictive of perioperative morbidity. Perioperative mortality was also associated with preoperative electrocardiographic findings and abnormal 2D echo parameters. In addition, systemic hypertension and operative variables were predictive of an increased duration of hospitalization after surgery.

Awareness of the preoperative clinical variables and diagnostic parameters identified in this study may assist the clinician in providing better risk assessment for patients with PH in preparation for noncardiac surgery. In addition, the various factors identified may also predict the prognosis and guide expectations for the patient with PH in terms of short-term morbidity, mortality, and LOS. Such insight may prompt the clinician to adopt a more aggressive approach in the hope of improving postoperative outcomes in this high-risk population.

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