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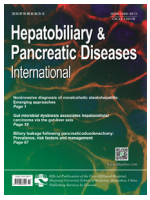

Original Article/Pancreas

Ventilation after pancreaticoduodenectomy increases perioperative mortality: Identification of risk factors and their relevance in Germany that do not apply in England

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ABSTRACT

Background: Pre-operative risk factors for post-operative ventilation and their influence on survival after pancreaticoduodenectomy for malignancy are unknown.
Methods: Totally 391 patients operated in Hannover, Germany were investigated with multivariable logistic regression and Cox regression modeling to identify independent risk factors for post-operative ventilation ≥6 h, patient survival and 90-day mortality. And 84 patients operated in Birmingham, United Kingdom were analyzed to assess the external relevance of findings.
Results: Longer operations, history of thrombosis, intra-operative blood transfusion, lower estimated glomerular filtration rates (eGFR) and higher values of the age at operation divided by the Horovitz Quotient independently increased the risk of post-operative ventilation ≥ 6 h in German patients ($n = 108$; 27.6%) ($P<0.050$). Blood transfusion and lower pre-operative eGFR levels increased the risk of early death in German patients significantly and independently of established prognostic factors. A history of thrombosis and lower eGFR levels were also independent significant risk factors for 90-day mortality in German patients but not in English patients. None of the English patients received post-operative ventilation. Significantly more German patients were >75 years, had a history of thrombosis, received blood transfusions, and had significantly worse lung function parameters. pT4 tumors were detected in 18 German patients (4.6%), but not in the English patients.
Conclusions: Identified risk factors for post-operative ventilation are clinically relevant in Germany but not in England and may be used to lower mortality risk. The German and the English cohorts displayed significant differences in the approach to patient selection and early post-operative extubation.

Introduction

Prolonged mechanical post-operative ventilation time is a significant risk factor for mortality in critically ill patients [1]. Many studies have examined specific causes of extended ventilation time. The main reason for prolonged ventilation after major surgery is that the patients are “too sick” [2]. This has two broad causes: either patients had pre-existing disease or mechanical ventilation causes diseases which make weaning more difficult. The risk for prolonged weaning is increased among patients with pulmonary diseases and amyosthenia leading to an overloaded thoracic musculature [3]. A working feedback mechanism and adequate muscle strength are essential for autonomous respiration [4]. Mechanical ventilation has many risks including exacerbation of cardiac insufficiency among patients with preexisting cardiac disease in whom pulmonary edema worsens respiratory function [3] and increases the frequency of infective complications such as pneumonia [5]. The incidence of pneumonia after surgery is reported between 1.2% and 4.6%, and hospital mortality is known to increase among patients with pneumonia to up to 28% [6].

A previous study proposed a potential prognostic model for the prediction of post-operative 90-day mortality and prolonged

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ventilation after liver transplantation using a respiratory risk score calculated after the first 24 h [7].

The impact of mechanical ventilation after pancreatoduodenectomy for malignancy on patient survival has so far not been analyzed extensively. This study identifies risk factors for post-operative artificial ventilation after pancreatoduodenectomy and their relevance for patient survival in a German cohort. Investigated candidate variables include pre-existing comorbidities, pre-operative laboratory variables and tumor-related variables with known influence on perioperative mortality as well as blood products given during the operation amongst others. This study further evaluates the relevance of identified risk factors in a different health care system in the United Kingdom in a cohort from a large English center in Birmingham with potentially relevant differences in clinical management.

Methods

Clinical setting

Data from two tertiary referral centers for hepato-pancreato-biliary surgery (Birmingham, UK and Hannover, Germany) was used for retrospective analysis.

Ethical considerations

Data collection and analysis were both carried out according to the latest version of the *Declaration of Helsinki*. All patients provided informed consent to scientific analysis of their data prior to hospital admission. All data was anonymized prior to analysis. This study was approved by the Ethics Committee of Hannover Medical School (reference number: 2979-2015).

German cohort for the identification of risk factors for post-operative ventilation (≥ 6 h) and survival

Pancreatic head resections performed due to malignancy at Hannover Medical School between 2000 and 2015 were analyzed retrospectively with the goal to identify independent risk factors for post-operative ventilation (≥ 6 h) and survival. All operations were elective surgeries with completed tumor resection. Exclusion criteria were operations for recurrent tumors, neuroendocrine tumors or other tumor entities. A total of 391 patients were included in the final German study cohort.

English cohort to assess the external relevance of findings

Pancreatic head resections performed due to malignancy at Queen Elizabeth Hospital Birmingham between 2015 and 2016 were analyzed retrospectively with the goal to validate externally the risk factors for post-operative ventilation (≥ 6 h) and survival identified in the German cohort and to assess the external relevance of findings. All operations were elective surgeries with completed tumor resection. Exclusion criteria were operations for recurrent tumors, neuroendocrine tumors or other tumor entities. The final study cohort comprised a total of 84 patients. Tumors were confirmed histologically after surgery as pancreatic adenocarcinoma ($n = 74$), adenocarcinoma of the ampulla Vateri ($n = 4$) or cholangiocarcinoma ($n = 6$).

Clinical data collection and definition of variables

Clinical data was collected retrospectively with ongoing data completion of follow-up data using patient files and established clinical information management systems. The duration of post-operative ventilation was defined as the time from when the last suture was placed to when ventilation was ceased. Post-operative ventilation times < 6 h have been observed in the first three quartiles of investigated German patients and were assumed to be likely clinically irrelevant.

All pre-operative variables were specified as the last available pre-operative data. The estimated glomerular filtration rate (eGFR) was calculated using the previously published MDRD study equation [8]. All investigated comorbidities were by definition pre-existent prior to surgery. The Horovitz-Quotient or oxygenation index has been defined as PaO_2/FiO_2 and is usually used to quantify lung function during anesthesia and in intensive care medicine [9]. The Horovitz-Quotient was used in this study as a variable which was based on the first intra-operatively available measurements.

Study endpoints

Study endpoints were defined as patient survival in years until death, 90-day mortality and post-operative mechanical ventilation after the end of pancreatic surgery ≥ 6 h.

Statistical analysis

Kaplan-Meier analyses and log rank tests were used for comparative survival analyses. In order to exclude survivorship bias as the consequence of early death due to post-operative complications we have repeated the Kaplan–Meier analysis after exclusion of 90-day mortality and stratified by < and ≥ 6 h of post-operative ventilation. Multivariable Cox regression modeling was used to determine independent risk factors for survival after pancreatic resection. Continuous variables were compared between patients with postoperative ventilation ≥ 6 h versus < 6 h using the Wilcoxon test while the Chi-squared test was used to compare binary data (data not shown). Multivariable logistic regression modeling was used to determine independent risk factors for prolonged post-operative ventilation ≥ 6 h.

Purposeful selection of covariates was used for the inclusion of variables into multivariable regression modeling using variables with a P value < 0.250 in univariate regression after exclusion of multicollinearity in principal component analysis. In cases of highly correlating variables ($R > |0.500|$) the decision on the inclusion versus the exclusion of highly correlating variables into multivariable modeling was made in favor of the inclusion of those variables with the lower P values or predominant clinical relevance as has been described before [10].

Potential factor interactions were assumed in multivariable regression modeling when parameter estimate changes of variables >20% occurred during the stepwise exclusion of statistically non-significant but clinically meaningful variables. Such observations prompted the generation and multivariable testing of interaction variables as has been described before [10]. Final multivariable regression models were reached when only statistically significant variables remained in multivariable modeling after stepwise backwards exclusion of the least significant variables with P values >0.050 [10].

Receiver operating characteristics (ROC) curve analysis with the determination of the area under the ROC curve (AUROC) was used to investigate the sensitivity and specificity of the final multivariable logistic regression model for the prediction of prolonged post-operative ventilation ≥ 6 h.

The identified independent risk factors for post-operative ventilation ≥ 6 h on patient survival were examined as potential independent risk factors for survival using multivariable Cox regression analysis. For this purpose, the variable post-operative ventilation ≥ 6 h was replaced by these identified independent predictors for prolonged ventilation in the previously defined final Cox regression model. Furthermore, multivariate logistic regression analysis was

used to determine identified risk factors for post-operative ventilation ≥ 6 h as independent risk factors for 90-day mortality in the German and English cohorts. *P* values < 0.050 were defined as significant. All statistical analyses were performed using JMP Pro 13 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics of the German cohort

The median age of the cohort was 66.5 years (range, 26.7–92.6 years) and 60.9% of the cohort were male. The median body mass index (BMI) was 25.1 kg/m^2 (range: 15.0–43.8). The median time on postoperative ventilation in the cohort of 391 patients was 2 h (range: 0–2034 h). The proportion of all patients with post-operative ventilation was 65.5%. Twenty-five percent of the ventilated patients were ventilated post-operatively for ≤ 1 h. The median duration of operation was 229 min (range: 101–478 min), and the median time on the intensive care unit was two days (range: 0–104 days). Median hospital stay was 23 days (range: 2–104 days). The 30-day mortality was 4.6% while 90-day mortality was 8.2% and hospital mortality was 6.4%. Two hundred and five patients (52.4%) received intra-operative transfusions of packed red blood cells with a median of 1 unit (range: 0–28 units) in the investigated cohort. Tumors were confirmed histologically after surgery as pancreatic adenocarcinoma ($n = 258$), adenocarcinoma of the ampulla Vateri ($n = 73$) or cholangiocarcinoma ($n = 60$). At resection, most patients had progressed tumors in T-stage pT3 (288, 73.7%). Intraoperative lymph node metastases were found in 234 patients (59.8%).

Post-operative ventilation ≥ 6 h reduces postoperative survival in the German cohort

Post-operative mechanical ventilation ≥ 6 h demonstrated amongst other factors a significant influence on post-operative survival as shown in Kaplan–Meier analysis (Fig. 1) as well as in the results of univariate (data not shown) and multivariate Cox regression analysis (Table 1). This significant influence of post-operative mechanical ventilation ≥ 6 h on survival was independent of known risk factors including the type of malignant tumor, the UICC 7 (2010) tumor stage, the pre-operatively eGFR, microscopically positive resection margins (resection status R1) and the pre-existing comorbidity cardiac arrhythmia (Table 1).

In order to exclude survivorship bias we repeated the Kaplan-Meier analysis after exclusion of 90-day mortality and stratified by < 6 h and ≥ 6 h of post-operative ventilation. The results of this analysis demonstrated that prolonged post-operative ventilation had no statistically significant influence on long-term survival after exclusion of 90-day mortality (Log-Rank-Test $P = 0.160$).

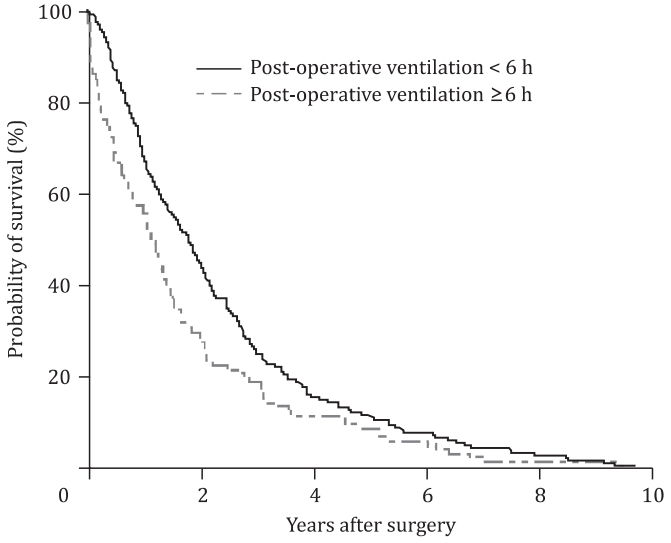

Fig. 1. Kaplan–Meier analysis of patient shows significantly shorter survival after post-operative ventilation ≥ 6 h (log-rank test: $P = 0.004$).

Identification of risk factors for post-operative ventilation ≥ 6 h in the German cohort

Univariable logistic regression analyses for the determination of risk factors for prolonged ventilation revealed that age at resection, the interaction variable age at operation divided by the Horovitz Quotient, reduced pre-operative eGFR rates, intra-operative transfusion of fresh frozen plasma, red blood cells or thrombocytes, number of revision operations, the pre-existing comorbidities cardiovascular diseases and a history of thrombosis all increased the risk for post-operative ventilation ≥ 6 h significantly (Tables 2 and 3).

Detection of independent risk factors for post-operative ventilation ≥6 h in the German cohort

The final multivariable logistic regression model revealed that the duration of the operation, a history of thrombosis, the

Table 1
The result of multivariable Cox-regression analysis in the German cohort performed to investigate the influence of postoperative ventilation ≥ 6 h (4th quartile) on patient survival after adjustment for previously known independent significant risk factors for postoperative survival.

Variables	HR	95% CI	*P* value	Distribution of variables
Type of tumor				
Periampullary carcinoma	Reference			73 (18.7%)
Cholangiocellular carcinoma	2.312	1.441–3.742	<**0.001**	60 (15.3%)
Pancreatic adenocarcinoma	2.937	1.979–4.488	<**0.001**	258 (66.0%)
UICC 7 (2010) stage[a]				
Stage IA	Reference			20 (5.3%)
Stage IB	2.087	0.913–4.770	0.069	37 (9.8%)
Stage IIA	2.068	0.973–4.393	**0.040**	87 (23%)
Stage IIB	3.371	1.613–7.045	<**0.001**	194 (51.1%)
Stage III	3.183	1.296–7.816	**0.011**	18 (4.8%)
Stage IV	6.384	2.720–14.983	<**0.001**	22 (5.8%)
Postoperative ventilation ≥ 6 h (4th quartile)	1.614	1.240–2.082	<**0.001**	108 (27.6%)
Pre-operative eGFR (μmol/L)	0.995	0.990–0.999	**0.030**	87.7 (10.1–192.2)
Microscopic tumor-free resection margin (R1 status)	1.738	1.181–2.481	**0.006**	39 (10.0%)
Pre-existing cardiac arrhythmia	1.635	1.120–2.317	**0.012**	42 (10.7%)

[a] Total population=378. The distribution of variables is shown by their frequencies and percentages for nominal variables and their median and range in brackets for continuous variables. HR: hazard ratio; 95% CI: 95% confidence interval, effect likelihood ratio test result; eGFR: estimated glomerular filtration rate.

Table 2
The results of univariable logistic regression analysis in the German cohort to determine the influence of variables on post-operative ventilation ≥ 6 h (4th quartile).

Variables	OR	95% CI	*P* value
Basic variables at resection			
Age at resection (yr)	1.031	1.008–1.055	**0.007**
Male sex	1.260	0.799–2.011	0.321
Body mass index (kg/m^2)	1.020	0.969–1.073	0.453
Pre-existing comorbidities			
Arterial hypertension	1.404	0.898–2.209	0.137
Heart failure	1.157	0.4337–2.795	0.758
Myocardial infarction	2.053	0.815–5.000	0.123
Cardiac arrhythmia	1.054	0.501–2.095	0.885
Cardiovascular diseases	2.003	1.129–3.511	**0.018**
Thrombosis	3.338	1.601–7.030	**0.001**
Coagulation disorder with higher risk of bleeding	1.707	0.804–3.507	0.160
Lipid metabolic disorder	1.385	0.766–2.447	0.276
Chronic inflammatory lung diseases	1.517	0.624–3.479	0.345
Structural lung diseases	0.652	0.033–4.468	0.692
Chronic renal failure	1.130	0.391–2.900	0.809
Hyperthyroidism	0.529	0.198–1.490	0.219
Rheumatism	0.285	0.015–1.541	0.165
Nicotine abuse	1.297	0.625–2.575	0.473
Alcohol abuse	0.706	0.158–2.316	0.588
Preoperative secondary malignant liver tumor	0.904	0.369–2.011	0.813
Hepatic cirrhosis	0.953	0.202–6.723	0.955
Toxic liver disease with cholestasis	0.549	0.181–1.374	0.211
Obesity	1.046	0.553–2.078	0.894
Diabetes	1.256	0.748–2.076	0.383
Diabetes type I	2.755	0.327–23.193	0.324
Diabetes type II	1.125	0.643–1.926	0.672
Pre-operative variables			
Bilirubin (mmol/L)	1.000	10.998–1.002	0.877
Creatinine (mmol/L)	1.007	1.000–1.015	**0.034**
Hematocrit (%)	0.997	0.944–1.053	0.908
Platelets (× 10^3/μL)	0.998	0.995–1.000	0.079
Potassium (mmol/L)	0.597	0.346–1.021	0.059
Quick-value (%)	0.984	0.970–0.999	**0.041**
Stenting of the ductus choledochus	0.988	0.620–1.590	0.960
Stenting of the ductus pancreaticus	1.276	0.175–6.639	0.783
eGFR (μmol/L)	0.990	0.981–0.999	**0.022**
Infiltration lymphatic pathway	1.054	0.651–1.688	0.828
Jaundice	0.851	0.499–1.484	0.564
Weight loss	1.300	0.825–2.048	0.257
Back pain	0.842	0.344–1.865	0.682

Significant results of the effect likelihood ratio test highlighted in bold letters. OR: odds ratio; 95% CI: 95% confidence interval; eGFR: Estimated glomerular filtration rate.

intra-operative transfusion of packed red blood cells, a pre-operatively reduced eGFR and the interaction variable age at operation divided by the Horovitz Quotient all had an independent significant influence on prolonged post-operative ventilation ≥ 6 h (Table 4). ROC curve analysis demonstrated an AUROC of 0.694 for the prediction of prolonged ventilation with this final logistic regression model (Fig. 2).

The resultant model has the following logit formula:

$$y = -1.634 + [0.007 \times \text{duration of the operation (min)}] + (0.521, \text{if pre} - \text{operative thrombosis, otherwise} - 0.521) + [2.286 \times (\text{age at operation/Horovitz Quotient})] + [-0.011 \times \text{eGFR}\ (\mu\text{mol/L}))] + (0.295, \text{if intra-operative transfusion of packed red blood cells, otherwise} -0.295)$$

Predictive factors for post-operative ventilation ≥ 6 h influence patient survival in the German cohort

Multivariable Cox regression showed that the intra-operative transfusion of packed red blood cells and the pre-operative eGFR were the only variables with a significant independent influence on prolonged ventilation (Table 4) that also have a significant influence on post-operative patient survival independent of the established prognostic factors in patients with pancreatic head

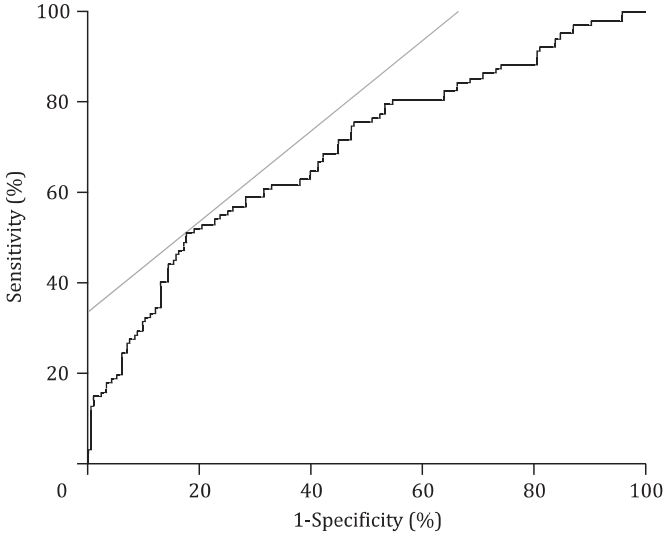

Fig. 2. The result of ROC-curve analysis with the area under the receiver operating curve (AUROC) for the prediction of post-operative ventilation ≥ 6 h (AUROC = 0.694).

Table 3
The results of univariable logistic regression analysis in the German cohort to determine the influence of variables on post-operative ventilation ≥ 6 h (4th quartile).

Variables	OR	95% CI	*P* value
Intra-operative variables			
Transfusion of fresh frozen plasma	2.979	1.787–4.968	**<0.001**
Number of fresh frozen plasma (units)	1.333	1.174–1.531	**<0.001**
Transfusion of packed red blood cells	2.740	1.717–4.453	**<0.001**
Number of packed red blood cells (units)	1.375	1.223–1.556	**<0.001**
Transfusion of thrombocyte concentrates	10.913	1.592–214.660	**0.014**
Number of thrombocyte concentrates (units)	6.777	1.482–128.812	**0.008**
Oxygen partial pressure (mmHg)	1.003	0.985–1.022	0.736
Fraction of inspired oxygen (%)	1.004	0.990–1.017	0.589
Horovitz Quotient (mmHg)	0.999	0.994–1.004	0.762
Age at resection in years/Horovitz-Quotient	1.418	1.009–1.993	**0.034**
Tumor variables			
Duodenum infiltration	0.641	0.409–1.000	0.050
UICC classification			
UICC Classification IA	Reference		
UICC Classification IB	1.269	0.369–4.357	0.703
UICC Classification IIA	1.015	0.331–3.117	0.979
UICC Classification IIB	1.070	0.370–3.093	0.900
UICC Classification III	1.909	0.477–7.638	0.357
UICC Classification IV	1.125	0.283–4.472	0.867
Grading			
Grading G1	Reference		
Grading G1-2	9.000	0.367–220.927	0.148
Grading G2	1.000	0.102–9.782	1.000
Grading G2-3	1.300	0.123–13.698	0.824
Grading G3	1.358	0.134–13.741	0.791
Largest tumor diameter (mm)	1.009	0.994–1.023	0.232
Microscopic vascular infiltration	1.328	0.744–2.316	0.331
Number of revision operations	3.850	2.603–6.036	**<0.001**
Type of tumor			
Periampullary carcinoma	Reference		
Cholangiocellular carcinoma	1.188	0.531–2.658	0.676
Pancreatic adenocarcinoma	1.516	0.819–2.804	0.175
Perineural sheath infiltration	1.014	0.649–1.584	0.953
Resection status			
Resection status R0	Reference		
Resection status R1	1.236	0.582–2.490	0.570
Resection status R2	2.780	0.109–70.727	0.480

Significant results of the effect likelihood ratio test highlighted in bold letters. OR: odds ratio, 95% CI: 95% confidence interval.

Table 4
The final multivariable logistic regression model in the German cohort with independent significant risk factors for ventilation ≥ 6 h after of pancreatic resection.

Variables	OR	95% CI	*P* value[a]
Duration of operation (min)	1.007	1.002–1.011	**0.001**
Pre-operative thrombosis	2.583	1.136–5.873	**0.013**
Intra-operative transfusion of packed red blood cells	1.875	1.094–3.214	**0.029**
eGFR (μmol/L)	0.989	0.979–0.999	**0.019**
Age at operation in years/Horovitz Quotient	13.394	1.169–153.507	**0.035**

[a] Effect likelihood ratio test results. OR: odds ratio; 95% CI: 95% confidence interval; eGFR: estimated glomerular filtration rate.

malignancy (Table 5). Post-operative ventilation ≥ 6 h also demonstrated a high and significant odds ratio for post-operative 90-day mortality in univariate logistic regression analysis (OR = 5.925; 95% CI: 2.747–12.776, $P < 0.001$).

Multivariable logistic regression analysis of the identified predictive factors for prolonged post-operative ventilation ≥ 6 h revealed that a history of thrombosis (OR = 3.246; 95% CI: 1.039–9.096, $P = 0.031$) and the eGFR (OR = 0.976; 95% CI: 0.960–0.993, $P < 0.006$) had both a significant independent influence on post-operative 90-day in the German cohort (Table 6).

Comparisons of the German and the English cohorts

Both cohorts demonstrated no statistically significant differences in patients' basic variables including age, sex, BMI, and pre-operative eGFR ($P > 0.050$) (Table 7). The comparison of the identified predictors for prolonged post-operative ventilation ≥ 6 h between the German and the English cohorts revealed that lung function as expressed in the Horovitz-Quotient was significantly worse in the German cohort. The German patients were ventilated with a significantly higher FiO_2 during surgery while the resulting arterial oxygen partial pressures were not significantly different in the English and German patients. The identified significant interaction variable age at resection divided by the Horovitz-Quotient was significantly higher in value in the German patients (Table 7). The transfusion of packed red blood cell was significantly less frequently deployed in the English cohort while the number of transfused units of packed red blood cells was significantly higher in the German cohort. The duration of operations was significantly shorter in the German cohort. The patients with a history of

Table 5
The result of multivariable Cox-regression analysis in the German cohort performed to investigate the independent influence of those variables with significant independent influences on postoperative ventilation ≥ 6 h (see also Table 4) on patient survival after adjustment for previously known independent significant risk factors for postoperative survival (see also Table 1).

Variables	HR	95% CI	*P* value
Type of tumor			
Periampullary carcinoma	Reference		
Cholangiocarcinoma	2.099	1.243–3.582	**0.006**
Pancreatic adenocarcinoma	2.706	1.747–4.330	**<0.001**
UICC 7 (2010) stage			
Stage IA	Reference		
Stage IB	2.583	0.974–6.849	**0.045**
Stage IIA	2.850	1.197–6.789	**0.008**
Stage IIB	4.602	1.963–10.790	**<0.001**
Stage III	4.941	1.829–13.354	**0.001**
Stage IV	9.718	3.600–26.241	**<0.001**
Duration of operation (min)	1.000	1.000–1.000	0.368
Intra-operative transfusion of packed red blood cells	1.434	1.098–1.729	**0.009**
Pre-operative thrombosis	1.122	0.693–1.729	0.584
Age at resection in years/Horovitz Quotient	1.100	0.894–1.315	0.349
Pre-operative eGFR (μmol/L)	0.995	0.990–1.000	**0.035**
Microscopic tumor-free resection margin (R1 status)	1.845	1.242–2.659	**0.003**
Pre-existing cardiac arrhythmia	1.620	1.086–2.339	**0.019**

HR: hazard ratio; 95% CI: 95% confidence interval, effect likelihood ratio test result. eGFR: estimated glomerular filtration rate.

Table 6
The final multivariable logistic regression model with independent significant risk factors for ventilation ≥ 6 h after of pancreatic resection and their influence on 90-days mortality in Hannover and Birmingham.

Variables	Hannover			Birmingham		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Duration of operation (min)	1.005	0.999–1.012	0.111	1.007	0.983–1.030	0.534
Intra-operative transfusion of packed red blood cells	1.063	0.360–3.890	0.917	9.000	0.260–932.340	0.203
Pre-operative thrombosis	3.246	1.039–9.096	**0.031**	0	0–34,921	0.927
eGFR (μmol/L)	0.976	0.960–0.993	**0.006**	0.917	0.762–1.004	0.090
Age at operation in years/Horovitz Quotient	1.342	0.812–2.087	0.228	0.091	0–5.302	0.552

Effect likelihood ratio test results; OR: odds ratio; 95% CI: 95% confidence interval. eGFR: estimated glomerular filtration rate.

Table 7
The results of descriptive statistics of the study cohort in Birmingham in comparison to the study cohort from Hannover.

Variables	Data Birmingham *n* (%) for binary data (median, range, *n* = 84)	Data Hannover *n* (%) for binary data (median, range, *n* = 391)	*P* value
Basic variables at resection			
Age at resection (yr)	68.2 (43.0–85.0)	67.8 (26.7–92.6)	0.782
Male	49 (58.3%)	238 (60.9%)	0.666
BMI (kg/m^2)	25.5 (15.6–43.6)	25.1 (15–43.8)	0.172
Pre-existing thrombosis	1 (1.2%)	32 (8.2%)	**0.022**
Pre-operative variables			
Creatinine (mmol/L)	70.0 (9.7–129.0)	70.0 (36.0–489.0)	0.613
Jaundice	67 (79.8%)	299 (76.4%)	0.893
eGFR (μmol/L)	85.8 (38.4–949.0)	87.7 (10.1–192.3)	0.298
Intra-operative variables			
Transfusion of red blood cells	11 (13.1%)	205 (52.4%)	**<0.001**
Number of packed red blood cells (units)	0 (0–4)	1 (0–28)	**<0.001**
Oxygen partial pressure (mmHg)	26.7 (3.7–68.4)	26.1 (5.1–82.4)	0.931
Fraction of inspired oxygen (%)	0.2 (0.2–0.5)	0.5 (0.2–1.0)	**<0.001**
Horovitz-Quotient (PaO_2/FiO_2)	127.1 (17.6–325.7)	56.0 (9.6–609.5)	**<0.001**
Age at resection/Horovitz-Quotient	0.5 (0.2–3.8)	1.2 (0.1–7.1)	**<0.001**
Tumor variables			
pT1	1 (1.2%)	21 (5.4%)	0.096
pT2	2 (2.4%)	63 (16.1%)	**<0.001**
pT3	81 (96.4%)	286 (73.1%)	**<0.001**
pT4	0	18 (4.6%)	**0.044**
pN1	67 (79.8%)	231 (59.1%)	**<0.001**
Periampullary carcinoma	4 (4.8%)	73 (18.7%)	**0.002**
Cholangiocarcinoma	6 (7.1%)	60 (15.3%)	**0.049**
Pancreatic adenocarcinoma	74 (88.1%)	258 (66.0%)	**<0.001**
Resection status R1	29 (34.5%)	39 (10.0%)	**<0.001**
Outcome			
30-day mortality	2 (2.4%)	18 (4.6%)	0.354
90-day mortality	2 (2.4%)	32 (8.2%)	0.060
Duration of operation (min)	274 (168–455)	229 (101–478)	**<0.001**

BMI: body mass index; eGFR: estimated glomerular filtration rate.

pre-existing thrombosis were significantly more frequent in the German cohort (Table 7). Patients with pT4 tumors were operated only in the German cohort. The percentage of patients operated with a pN1 status was significantly higher in the English cohort while the percentage of patients with R1 resections with a histologically positive resection margin was significantly higher in the English cohort (Table 7). The 30-day mortality in the English cohort was 2.4% while 30-day mortality in the German cohort was 4.6% ($P=0.354$, Table 7). The 90-day mortality was 2.4% in the English cohort and 8.2% in the German cohort, almost reaching statistical significance ($P=0.060$, Table 7).

Validation of predictive factors for post-operative ventilation ≥ 6 h and mortality in the English cohort

A validation of the predictive factors for post-operative ventilation ≥ 6 h was impossible with data from Birmingham due to a complete lack of cases with post-operative ventilation ≥ 6 h.

Multivariable logistic regression analysis with identified predictors for prolonged ventilation ≥ 6 h after surgery in the German cohort revealed that not even one of these factors had an independent significant influence on post-operative 90-day mortality in the English cohort (Table 6).

Discussion

This is the first study which shows that even a comparatively short prolonged duration of post-operative artificial ventilation ≥6 h after pancreatic head resection for malignancy constitutes a significant risk factor for short-term post-operative patient survival in a German cohort (Fig. 1). Post-operative ventilation ≥ 6 h has further been revealed in this study as a significant independent risk factor for early post-operative death which was independent of established risk factors [11,12] including UICC stage, type of malignant tumor, tumor-free resection margins, and pre-existing comorbidities such as compromised kidney function and cardiac arrhythmia (Table 1). However, such prolonged ventilation could not be validated as a risk factor for survival in the cohort from Birmingham which is due to the fact that none of these patients were post-operatively ventilated. This is a major finding of this study that points to relevant differences in the surgical approach to pancreatic malignancy between the participating English and German centers.

Furthermore, this study clearly demonstrates that a preoperative history of thrombosis and lower eGFR values prior to resection not only increases the risk of prolonged post-operative ventilation ≥6 h in the German cohort but also increase the risk of post-operative 90-day mortality independently and significantly. These risk factors for post-operative ventilation could of course not be validated in the English cohort, because none of the English patients was ventilated post-operatively. Direct comparison of the German and the English patients revealed that amongst these factors only the frequency of a history of pre-operative thrombosis is significantly different (lower) in the English cohort which may potentially be a consequence of underreporting or, alternatively a major so far undetected difference in pre-operative comorbidity (Table 7).

The comparatively higher 90-day mortality rate in the German cohort (8.2% versus 2.4%) did not reach statistical significance and may at least partially be due to a higher recurrence rate of the underlying malignant disease, because pT4 tumors were only operated in the German cohort and not in the English cohort. This notion is underlined by the observation that the patients operated with pT4 tumors in the German cohort ($n=18$, 4.6%) displayed a 90-day mortality rate of 11.1%. This observation seems to be in line with the previously published observation by the Pancreatic Surgery Mortality Study Group that 90-day mortality rates of 5% after major pancreatic surgery are assumed to be due to recurrent malignancy [13]. The fact that the patients in the English cohort were operated more recently (2015–2016) as compared to the German cohort (2000–2015) may further partially explain the higher observed early post-operative mortality rates after resection in the German cohort, since it is widely accepted that recent advances in perioperative management have decreased post-operative early mortality substantially in the UK [14].

It is noteworthy that 22.3% of the German cohort was older than 75 years ($n=87$) which was associated with a 90-day mortality rate of 11.5% while only 13.1% of the English cohort ($n=11$) was older than 75 years which was associated with an absent 90-day mortality rate (0%). This difference points to different attitudes to major pancreatic surgery in the elderly with a probably much more careful indication for major surgery in older patients in the English cohort. This notion is further underlined by a report from the UK where only 0.2% of the patients older than 85 years with pancreatic cancer had an operation [15], while 1.8% of patients were older than 85 years in the German cohort. These observations may provide further hints to the reasons for the observed differences between the German and the English cohorts in 30-day as well as 90-day mortality rates. Justified discrimination against old age clearly remains a topic for debate in pancreatic surgery with far reaching ethical implications.

It is most striking in this study that prolonged ventilation after surgery ≥ 6 h has not been observed in the English cohort. It is very likely that substantially different perioperative management approaches in the investigated German and English cohorts play an important role here. For example, the likelihood of intra-operative blood transfusions was significantly higher in German patients while German patients suffered from a more severe morbidity burden as indicated more frequent previous thrombosis and worse intra-operative lung function test results (Horovitz-Quotient). This shows that intraoperative ventilation with significantly higher FiO_2 values was used in the German cohort in order to reach similar arterial partial oxygen pressures (Table 7).

Further, the frequency of far advanced tumors (pT4) was also significantly higher in the German cohort while operating time was significantly shorter. This is probably due to relevant differences in the surgical attitude towards the indication for pancreaticoduodenectomy in patients with advanced malignant pancreas tumors. The significantly longer operations in the English cohort may indicate a more careful surgical approach during the operation which may contribute to the observed less frequent deployment of intraoperative blood transfusions.

Taken together, these findings underline the notion that the identified risk factors for prolonged ventilation in the German cohort are obviously not relevant in the English cohort. However, we still consider the identified risk factors in the German cohort as clinically plausible risk factors for prolonged post-operative ventilation as argued below. It is noteworthy in this context that the number of patients who were post-operatively ventilated ≥ 6 h decreased in Hannover significantly during the study period (Fig. 3).

Post-operative ventilation ≥ 6 h increases the risk of post-operative pneumonia which is probably the reason why such prolonged ventilation is an independent risk factor for survival in this study. Age and respiratory causes have recently been described as predicting factors for failure in weaning by Shin et al. [16]. In their study, the authors identified pneumonia as the main respiratory risk factor for prolonged ventilation while prolonged ventilation itself increases the risk for pneumonia which leads to an increased risk of early death after major surgery [5, 6]. Comorbidities have previously been described as risk factors for mortality after major pancreatic resection [13]. Post-operative ventilation has been shown as a significant risk factor for mortality due to organ

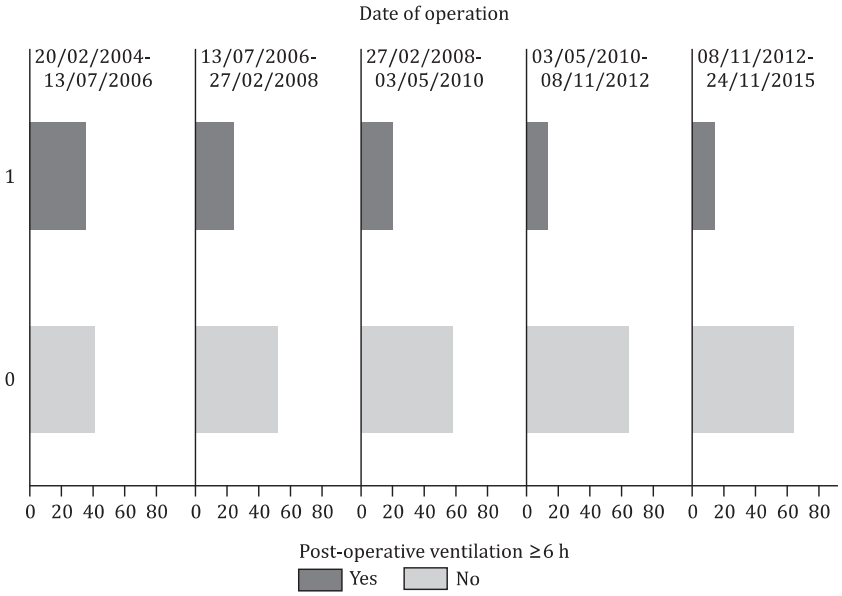

Fig. 3. The significantly decreasing numbers of patients, who were ventilated in Hannover for ≥ 6 h after surgery during the investigated period of time ($P<0.001$, logistic regression analysis, numbers indicate the number of patients and not proportions in % while the graphic representation illustrates the changes in relative proportions graphically).

failure increasing mortality risk by 3.3% per day for patients treated for more than 30 days in intensive care after different types of surgery [17].

Risk associated with intra-operative transfusion of packed red blood cells

The lack of intra-operative blood transfusion has been reported to be associated with better long-term survival after pancreas resection for ductal adenocarcinoma [18]. Transfusion-related acute lung injury (TRALI) after transfusion of fresh frozen plasma or transfusion of platelet concentrates has been shown to be associated with increased morbidity and mortality [19]. Further, Parson et al. [20] described a link between the transfusion of red blood cells in critically ill patients and subsequent reduction of muscle strength which has been implicated in failure of weaning from ventilation. It is therefore no surprise that the intra-operative transfusion of packed red blood cells has been identified in this study as an independent risk factor increasing the risk for both, prolonged post-operative ventilation ≥6 h and shorter patient survival (Tables 4 and 5).

Risk associated with compromised renal function with lower eGFR levels

Even mildly compromised renal function is known to be associated with a higher risk of postoperative complications and higher mortality rates after surgery [21]. Further, acute kidney injury has been associated with more difficult weaning [22]. Johnson et al. [23] previously demonstrated that a pre-operatively elevated creatinine level above 1.5 mg/dL is an independent predictor for respiratory complications after general and vascular surgery. In contrast to our study, respiratory complications were defined in their study as post-operative ventilation longer than 24 h. Their study has shown that both acute renal injury and a moderate degenerative change in renal function have an impact on prolonged post-operative ventilation time [23]. In this context it is noteworthy that older patients, who are known to be more difficult to wean from artificial ventilation [16] have typically also lower physiological eGFR values as compared to younger patients which indicates a declining renal function during aging [24]. It is therefore intuitive that lower eGFR has been identified in this study as an independent risk factor for both post-operative ventilation ≥ 6 h and shorter patient survival (Tables 4 and 5).

The role of the Horovitz-Quotient as an expression of pre-existing lung function

The Horovitz-Quotient or oxygenation index (PaO_2/FiO_2) is used in intensive care medicine to describe lung function in artificially ventilated patients [9]. Physiologically, lung capacity decreases with age [25]. Strikingly, the pre-operative interaction variable which was identified in this study for the first time as age at operation divided by the Horovitz-Quotient is shown here as a significant independent risk factor for post-operative ventilation ≥ 6 h. This observation is clinically intuitive since older patients with lower Horovitz Quotients can be expected to suffer from compromised lung function due to less efficient gas exchange potentially leading to failure of weaning when compared to younger patients with higher Horovitz Quotients [7,26]. Kleine et al. have demonstrated previously that a pre-operative Horovitz Quotient of less than 200 mmHg is an independent risk factor for prolonged ventilation and patient survival after liver transplantation [7].

The role of thrombosis

A preoperatively diagnosed thrombosis has been identified in this study as an independent risk factor for post-operative prolonged ventilation. A possible explanation for this observation may be an increased risk of *de novo* thrombosis and lung embolism in those patients with a previous history of thrombosis as has been described before [27]. Micro thrombosis in peripheral veins followed by subclinical lung embolism may be more likely in patients with a history of previous thrombosis [28].

Further, patients with an adenocarcinoma and elevated preoperative D-dimers are known to have a significantly shorter survival. Preoperative D-dimer is a biomarker for the survival prediction of pancreatic adenocarcinoma [29]. Thrombosis and cancer are closely linked by various pathophysiological mechanisms and cancer increases the risk for thrombosis [30]. It has been estimated that

20%–30% of all first venous thromboembolic events are cancer related [31].

In a paper by Johnson et al. [23], pre-operatively diagnosed bleeding disorders have been described as an independent risk factor for respiratory complications after general and vascular surgery. Interestingly, in the current study bleeding disorders leading to a higher risk of bleeding did not have any statistically significant influence on prolonged ventilation which may hint to careful surgical technique.

The role of the operation duration

Mechanical ventilation is a risk factor for lung injury itself [32]. Consequently, longer operation time increases the risk for ventilation-associated lung injury including a higher likelihood of post-operative pneumonia [5]. Longer operations can also be associated with more difficult surgery, more bleeding and intra-operative difficulty and therefore potentially a need for longer post-operative ventilation. However, none of the English patients was ventilated while the duration of the operations was significantly longer in the English cohort. Therefore we assume some confounding which probably includes a more aggressive approach to extubation in the operating theatre in Birmingham.

Clinical usefulness of the findings of this study

This study demonstrates that the derived multivariable models provide powerful tools for a clinically relevant international comparison of treatment approaches between treatment units. This study is therefore seen as a contribution to the establishment of data-driven benchmarks in pancreatic surgery. Further, estimating expected post-operative outcomes helps to improve prognostic decision-making with the goal to find the best individual therapeutic options. The insights provided by this study may to some degree inform the counseling of individual patients based on individual risk factors while clearly emphasizing the benefits of early extubation after pancreatic surgery.

Relevance of organizational aspects and resultant perioperative management

We believe that the awareness of the advantages of early extubation in the operating theatre is lacking in Germany due to abundantly available intensive care beds when compared to other European countries. This limits external validation of identified risk factors for the prediction of prolonged post-operative ventilation $\geq$6 h. Pearse et al. [33] have shown that the proportion of German patients who went to intensive care units after general surgery is one of the highest in Europe, reaching a total of 11.6% [33].

This study highlights several major differences in perioperative management between both centers in Germany and England that include also different approaches to the discrimination against old age.

Limitations

One of the limitations of this study is its retrospective design which limits the level of achievable evidence due to lack of randomization. A further caveat is that the decision in favor of mechanical ventilation after the end of surgery on the intensive care unit is probably not only made due to medical reasons but may also depend on the proximity of the end of surgery to the typical knocking-off time of anesthesiologists between 16:00 h and 17:00 h and abundant availability of intensive care beds in Germany. Similar observations have been shown before [34]. The influence of the time of the end of surgery on prolonged post-operative ventilation has not been analyzed in this study and should be the focus of another study. Data on pre-operative lung function parameters assessed by lung function tests would be highly desirable. Due to the retrospective nature of our study, there was not sufficient data available on pre-operative lung function tests, because these tests have not been routinely performed prior to surgery. Furthermore, while the number of deaths caused by respiratory failure would be interesting to know, it is most difficult to assign such a specific cause of death to all cases with mortality correctly in a retrospective study. It is almost impossible to differentiate in patients who died due to sepsis the proportion of patients who developed sepsis due to pneumonia from other causes of sepsis. Therefore we have decided against analyzing death caused by respiratory dysfunction as a study end-point.

Conclusions

This study demonstrates the relevance of reducing or avoiding post-operative ventilation after pancreatic head resection for malignancy with the goal to improve survival. With this goal in mind the requirement for intra-operative blood transfusions should be avoided by careful bloodless surgical technique and the duration of the operation should be limited. Older patients with a lower Horovitz-Quotient, a history of thrombosis and a lower eGFR should be operated by the most experienced surgeons to improve the risk profile for prolonged post-operative ventilation by reducing the duration of the operation and by the avoidance of required blood transfusions. Patients with increased likelihood of predicted prolonged post-operative ventilation $\geq$ 6 h may benefit from improved post-operative monitoring and early successful extubation. Pre-operative lung function tests are desirable to improve patient safety.

Contributors

SH proposed the study. HRS and SH performed the research and wrote the first draft. HRS and RKJ collected the data. HRS and SH analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. SH is the guarantor.

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Ethical approval

This study was approved by the Ethics Committee of Hannover Medical School (reference number: 2979-2015).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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