Supplementary Materials

Title:

Time-varying mortality risk after gastrointestinal surgery complicated by postoperative infections:

A Danish Nationwide study of 859,766 patients

Authors:

Doruk Orgun, M.D., Ask Tybjærg Nordestgaard, M.D., Ph.D., Rasmus Peuliche Vogelsang, M.D.,

Ph.D., Henrik Enghusen Poulsen, M.D., D.M.Sci., Christina Ellervik, M.D., D.M.Sci., Ismail

Gogenur, M.D., D.M.Sci.

Index:

Supplementary Table 1: List of International Classification of Diseases, 10th Revision (Danish version) codes that were utilized in the study to capture postoperative infections.

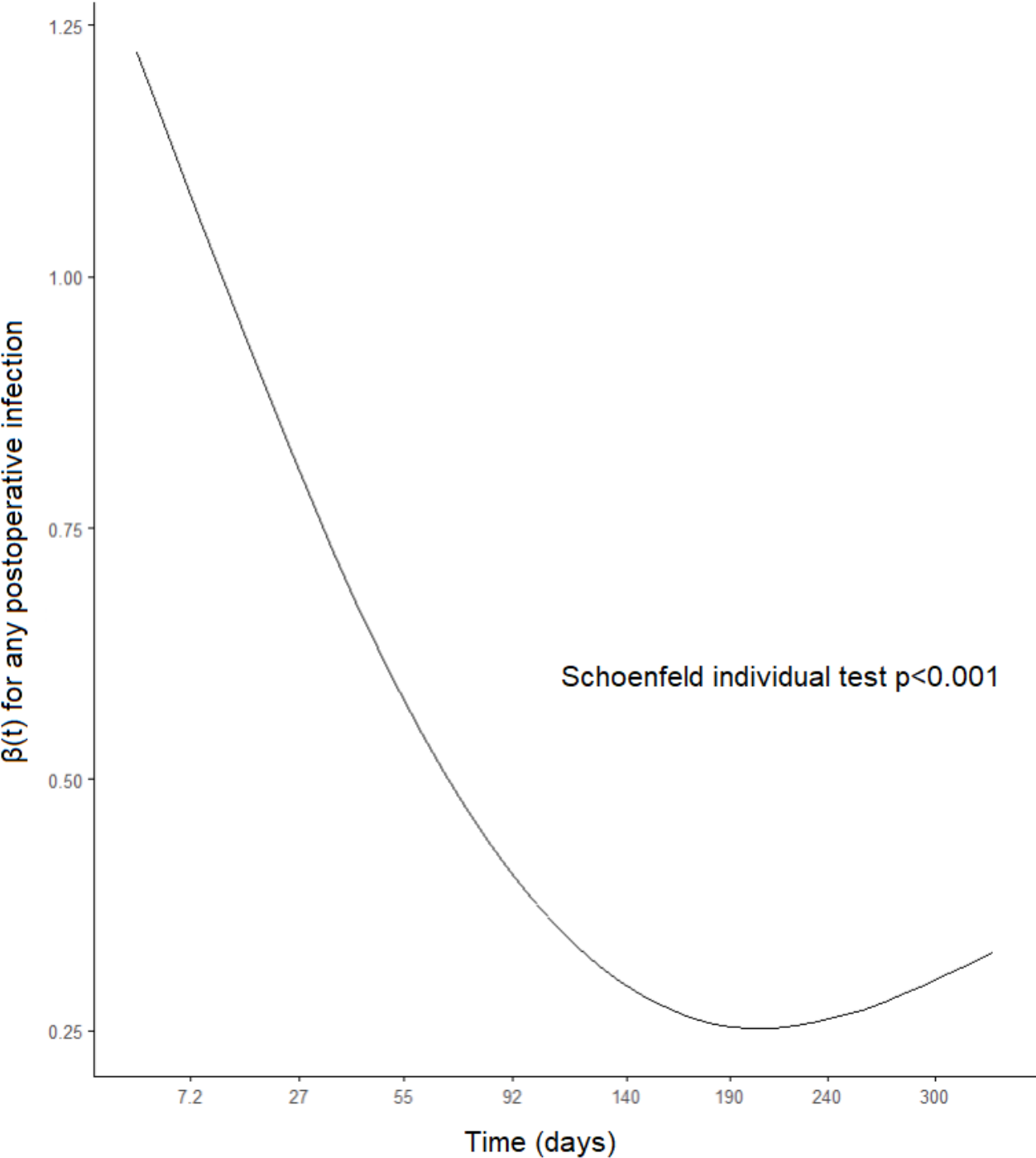| Postoperative infection type	Danish ICD-10 codes*
Surgical site infections	T81.4A-T81.4C, T81.4E-T81.4J, K65, K75.0, L02.2, L03, L08, M60.8A, A48.0
Pneumonia	J12-J18, A31.0, A48.1, T81.4P
Urinary tract infections	N10, N30.0, N30.9, T81.4U
Sepsis/bloodstream infections	A39.2, A40–A41, A02.1, A20.7, A22.7, A26.7, A32.7, A42.7, A48.3, A54.8G, A49.9A, B37.7, I33, I38-I39, J95.0A, T80.2D, T82.6, T81.4D

Supplementary Table 2: Causes of death within the study cohort according to 30-day postoperative infection status

Cause of death[*], n (%)	No 30-day postoperative infection (n = 834,640)	Any 30-day postoperative infection (n = 25,126)	Total (n = 859,766)	*P* value[**]
Infection	312 (0.7)	85 (2.5)	397 (0.9)	<0.001
Cardiovascular	2603 (6.6)	262 (7.7)	2865 (6.7)	0.02
Cancer	27,155 (69.3)	1673 (49.2)	28,828 (67.7)	<0.001
Pulmonary	1302 (3.3)	262 (7.7)	1564 (3.7)	<0.001
Gastrointestinal	2738 (7.0)	502 (14.8)	3240 (7.6)	<0.001
Cerebrovascular or dementia	1416 (3.6)	157 (4.6)	1573 (3.7)	0.003
Urogenital	371 (0.9)	63 (1.9)	434 (1.0)	<0.001
Other	3312 (8.4)	399 (11.7)	3711 (8.7)	<0.001
Total	39,209	3403	42,612	

* Defined by the ICD-10 code that was captured as the primary cause of death in the Danish Causes of Death Registry. Corresponding codes: *Infection (A00-B99), Cardiovascular (I00-52, I70-I79), Cancer (C00-C97, D00-D09), Pulmonary (J00-J99), Gastrointestinal (K00-K93), Cerebrovascular or dementia (F03.9, I60-I69, R54), Urogenital (N00-N99)*

** P values were calculated using Pearson's chi-squared test with two-sided P values less than 0.05 were considered as statistically significant. The frequencies of cause of death types to the total number of deaths were used to populate the contingency tables.

Supplementary Figure 1: Plot of changes in β-coefficient values between postoperative days 30 and 365 for any postoperative infection as a predictor for mortality. Scaled Schoenfield residuals over time are not shown due to Statistics Denmark's regulations.

Supplementary Table 3: Adjusted hazard ratios for mortality at postoperative day 30 for the remaining of the follow-up (until postoperative day 365) as calculated by the multivariable Cox regression model for all covariables included for adjustment.

Variable	Adjusted hazard ratio for mortality [95% CI]	P-value*
Any postoperative infection		
No	*Reference*	
Yes	2.25 [2.13 – 2.38]	<0.001
Age	1.04 [1.04 – 1.04]	<0.001
Sex		
Female	*Reference*	
Male	1.00 [0.98 – 1.02]	<0.001
Procedure type (stratification) [a]		
Open abdominal wall/hernia [b]	*Reference*	
Laparoscopic abdominal wall/hernia	-	
Open lower GI	-	
Laparoscopic lower GI	-	
Open upper GI	-	
Laparoscopic upper GI	-	
Open hepato-pancreato-biliary	-	
Laparoscopic hepato-pancreato-biliary	-	-
Hospital region		
Copenhagen	*Reference*	
Fyn	1.07 [1.04 – 1.11]	<0.001
Jutland	0.98 [0.96 – 1.00]	0.10
Zealand	0.98 [0.94 – 1.01]	0.15
Emergent surgery [a]		
No	*Reference*	
Yes	-	-

Reoperation		
No	*Reference*	
Yes	1.27 [1.19 – 1.35]	<0.001
Year of surgery		
1996-2000	*Reference*	
2001-2005	0.89 [0.87 – 0.91]	<0.001
2006-2010	0.85 [0.83 – 0.88]	<0.001
2011-2015	0.76 [0.74 – 0.78]	<0.001
2016-2018	0.72 [0.69 – 0.75]	<0.001
Perioperative GI cancer diagnosis [a]		
No	*Reference*	
Yes	-	-
Postoperative length of stay	1.00 [1.00 – 1.00]	
Diabetes		
No	*Reference*	
Yes	1.33 [1.30 – 1.37]	<0.001
Cancer history [a]		
No	*Reference*	
Yes	-	-
Coronary artery disease		
No	*Reference*	
Yes	1.01 [0.98 – 1.04]	0.37
Heart failure		
No	*Reference*	
Yes	1.45 [1.40 – 1.51]	<0.001
Dialysis history		
No	*Reference*	
Yes	1.33 [1.30 – 1.37]	<0.001
Cerebrovascular disease		
No	*Reference*	

Yes	1.28 [1.23 – 1.32]	<0.001
Obstructive pulmonary disease		
No	*Reference*	
Yes	1.43 [1.38 – 1.48]	<0.001
Cirrhosis		
No	*Reference*	
Yes	2.93 [2.77 – 3.10]	<0.001

[a] Strata adjustment method was utilized for marked variables since the hazards of marked variables were not proportional over time. Thus, hazard ratios for mortality cannot be estimated for these variables.

[b] Open abdominal wall/hernia group is taken as reference due to being the procedure type with the highest number of occurrences.

Supplementary Table 4: Sensitivity analyses - adjusted hazard ratios for mortality for postoperative days 30-365, 91-365, 181-365, and 271-365 according to 30-day postoperative infection status after a) excluding patients without an infection diagnosis on the day of admission for surgery, b) stratification for hospital codes, c) excluding postoperative length of stay variable for adjustment

Adjusted hazard ratios for mortality* [95% CI]				
	Postoperative days 30-365	**Postoperative days 91-365**	**Postoperative days 181-365**	**Postoperative days 271-365**
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Main cohort (all patients)				
Any infection	2.25 [2.13 – 2.38] *p<0.001*	1.88 [1.74 – 2.04] *p<0.001*	1.44 [1.29 – 1.62] *p<0.001*	1.11 [1.00 – 1.28] *p<0.05*
Patients without an infection diagnosis on the day of admission				
Any infection	2.25 [2.13 – 2.38] *p<0.001*	1.89 [1.74 – 2.05] *p<0.001*	1.45 [1.29 – 1.64] *p<0.001*	1.16 [1.01 – 1.35] *p<0.05*
Patients stratified for hospital				
Any infection	2.35 [2.20 – 2.51] *p<0.001*	1.98 [1.80 – 2.17] *p<0.001*	1.52 [1.33 – 1.74] *p<0.001*	1.18 [1.02 – 1.40] *p<0.05*
Without adjustment for postoperative length of stay				
Any infection	2.25 [2.13 – 2.38] *p<0.001*	1.89 [1.75 – 2.04] *p<0.001*	1.45 [1.30 – 1.63] *p<0.001*	1.12 [1.00 – 1.30] *p<0.05*

* Cox regression models were adjusted for age, sex, surgery-specific co-variables (procedure type, elective/emergent surgery, reoperation, year of surgery, perioperative GI cancer diagnosis, hospital area, postoperative length of stay) and patient comorbidities. CI: confidence interval.

Supplementary Table 5: Subgroup time-specific adjusted hazard ratios for mortality for postoperative days 30-365, 91-365, 181-365, and 271-365 according to 30-day postoperative infection status

Adjusted hazard ratios for mortality [*] [95% CI]			
	Postoperative days 30-365	**Postoperative days 91-365**	**Postoperative days 181-365**	**Postoperative days 271-365**
Main cohort (all patients)				
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection	2.25 [2.13 – 2.38] *p<0.001*	1.88 [1.74 – 2.04] *p<0.001*	1.44 [1.29 – 1.62] *p<0.001*	1.11 [1.00 – 1.28] *p<0.05*
Perioperative GI cancer diagnosis status				
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection, no perioperative GI cancer diagnosis	2.66 [2.49 – 2.84] *p<0.001*	2.22 [2.02 – 2.44] *p<0.001*	1.69 [1.47 – 1.94] *p<0.001*	1.29 [1.07 – 1.55] *p<0.05*
Any infection, perioperative GI cancer diagnosis	1.54 [1.39 – 1.70] *p<0.001*	1.35 [1.18 – 1.55] *p<0.001*	1.11 [0.91 – 1.35] *p>0.05*	0.91 [0.70 – 1.18] *p>0.05*
Age group				
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection, age <65	2.19 [1.96 – 2.44] *p<0.001*	1.86 [1.60 – 2.16] *p<0.001*	1.46 [1.17 – 1.81] *p<0.001*	1.14 [0.86 – 1.52] *p>0.05*
Any infection, age ≥65	2.27 [2.13 – 2.42] *p<0.001*	1.89 [1.72 – 2.07] *p<0.001*	1.44 [1.26 – 1.64] *p<0.001*	1.05 [0.88 – 1.25] *p>0.05*

Emergent surgery or non-emergent surgery				
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection, emergent surgery	1.91 [1.78 – 2.04] *p<0.001*	1.64 [1.46 – 1.81] *p<0.001*	1.30 [1.13 – 1.50] *p<0.001*	1.04 [0.86 – 1.25] *p>0.05*
Any infection, non-emergent surgery	2.47 [2.25 – 2.71] *p<0.001*	2.08 [1.83 – 2.37] *p<0.001*	1.61 [1.34 – 1.93] *p<0.001*	1.24 [0.98 – 1.57] *p>0.05*

* Cox regression models were adjusted for age, sex, surgery-specific co-variables (procedure type, elective/emergent surgery, reoperation, year of surgery, perioperative GI cancer diagnosis, hospital area, postoperative length of stay) and patient comorbidities. CI: confidence interval.

Supplementary Table 6: Sensitivity Cox regression analyses that utilized landmark times of 10 and 20 days.

Adjusted hazard ratios for mortality [*] [95% CI]				
Main analysis **(Landmark analysis with exclusion of patients** **who died in the first 30 postoperative days)**				
	Postoperative days 30-365	**Postoperative days 91-365**	**Postoperative days 181-365**	**Postoperative days 271-365**
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection	2.25 [2.13 – 2.38] *p<0.001*	1.88 [1.74 – 2.04] *p<0.001*	1.44 [1.29 – 1.62] *p<0.001*	1.11 [1.00 – 1.28] *p<0.05*
Landmark analysis with exclusion of patients **who died in the first 20 postoperative days**				
	Postoperative days 20-365	**Postoperative days 91-365**	**Postoperative days 181-365**	**Postoperative days 271-365**
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection	2.39 [2.26 – 2.52] *p<0.001*	1.89 [1.74 – 2.05] *p<0.001*	1.40 [1.24 – 1.57] *p<0.001*	1.03 [0.88 – 1.20] *p>0.05*
Landmark analysis with exclusion of patients **who died in the first 10 postoperative days**				
	Postoperative days 10-365	**Postoperative days 91-365**	**Postoperative days 181-365**	**Postoperative days 271-365**
No infection	*Reference*	*Reference*	*Reference*	*Reference*
Any infection	3.00 [2.83 – 3.18] *p<0.001*	2.18 [1.98 – 2.39] *p<0.001*	1.51 [1.31 – 1.74] *p<0.001*	1.05 [0.87 – 1.26] *p>0.05*

[*] Cox regression models were adjusted for age, sex, surgery-specific co-variables (procedure type, elective/emergent surgery, reoperation, year of surgery, perioperative GI cancer diagnosis, hospital area, postoperative length of stay) and patient comorbidities. CI: confidence interval.