International Journal of Surgery 72 (2019) 47–54

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Laparoscopic repair of perforated peptic ulcer is not prognostic factor for 30-day mortality (a nationwide prospective cohort study)

Sergej Zogovic[a,*], Anders Bo Bojesen[b], Shadi Andos[a], Frank Viborg Mortensen[c]

[a] Surgical Department, Hospital of Southern Jutland, Aabenraa, Denmark
[b] VIVE – the Danish Center for Social Science Research, Denmark
[c] Department of Surgical Gastroenterology, Aarhus University Hospital, Denmark

ARTICLE INFO

Keywords:
Laparoscopic surgery
Perforated peptic ulcer
Risk factors
Mortality

ABSTRACT

Background: Laparoscopic surgery has become increasingly popular in treating perforated peptic ulcer (PPU). However, currently it is not recognized as a prognostic factor for mortality within this group of patients. The aim of this study was to investigate whether laparoscopic surgery was an independent mortality risk factor in patients treated surgically for perforated peptic ulcer.

Materials and methods: This was a Danish nationwide cohort study based on prospectively collected data of 1008 patients treated surgically for PPU between September 2011 and December 2015. A propensity score matching analysis, considering most of the known prognostic factors for mortality and baseline characteristics, was used to adjust mortality estimates in patients treated with open and laparoscopic surgery. The primary outcome was postoperative 30-day mortality.

Results: The study population comprised 1008 patients; 507 were treated laparoscopically and 501 by open surgery. There was significantly higher mean age, and higher ASA scores, as well as other mortality risk factors in the open surgery group. The unadjusted 30-day mortality was significantly lower in patients undergoing laparoscopic surgery compared to open surgery (HR = 0.48, 95% CI: 0.36–0.65). After matching and weighting controls, the adjusted difference in mortality was reduced and was not significant (HR = 0.82, 95% CI: 0.59–1.15). The 30-day mortality was 13.1% for laparoscopy and 14.7% for the matched controls in the open surgery group.

Conclusions: Compared to open surgery, laparoscopic surgery in patients with PPU does not reduce short term mortality. More well powered randomized clinical trials are needed to investigate the role of laparoscopic surgery in treatment of patients with PPU.

1. Introduction

The incidence of perforated peptic ulcer (PPU) has decreased during past two decades. Despite advances in critical care and treatment of PPU, the reported mortality is as high as 27% in some countries [1–3].

A number of prognostic factors were identified to predict short term mortality in patients with PPU [4,5]. Those factors were used as a basis for four scoring systems that predict outcome in patients with PPU, in addition to several others non-disease specific outcome scores [6]. Laparoscopic treatment is currently not recognized as a prognostic factor for mortality.

Since the introduction of laparoscopic surgery for PPU in 1990 [7], it has been increasingly used in the treatment of PPU, a serious complication of peptic ulcer [8]. Current data support laparoscopic surgery is as effective as open surgery, with the known benefits of a lower rate of surgical site infections, less postoperative pain and shorter nasogastric tube duration [9]. Laparoscopic surgery is recommended by some surgical societies as the primary surgical approach for PPU [10].

The aim of this study was to investigate if laparoscopic repair of PPU is an independent prognostic factor for mortality in the Denmark national cohort over a period of five years (2011–2015).

2. Methods

2.1. Study design

This was a national cohort study of prospectively collected data from patients treated surgically for PPU. Data were collected from 25

* Corresponding author. Sygehus Sønderjylland, Kresten Philipsens Vej 15, 6200, Aabenraa, Denmark.
E-mail addresses: sergej.zogovic@rsyd.dk (S. Zogovic), anders@socioskop.dk (A.B. Bojesen), shadi.andos1@rsyd.dk (S. Andos), franmort@rm.dk (F.V. Mortensen).

https://doi.org/10.1016/j.ijsu.2019.10.017
Received 8 August 2019; Received in revised form 3 October 2019; Accepted 17 October 2019
Available online 19 October 2019

hospitals in Denmark between September 2011 and December 2015. There was no age limitation.

The study was approved by the Danish Data Protection Agency through the Data Inspectorate for Clinical Quality Databases approved by Statens Serum Institut.

The study was conducted in accordance with guidelines for Strengthening the reporting of cohort studies in surgery (STROCSS) [11].

2.2. Study population and data

All patients surgically treated for PPU in Denmark between September 2011 and December 2015 were included. Patients who had open surgery following laparoscopic surgery were excluded from the study. In Denmark, the treatment of abdominal emergencies, including PPU, is only provided by public hospitals. In 2003, Danish public healthcare authorities established the Danish Clinical Register of Emergency Surgery (DCRES), now part of The Danish Clinical Registries (RKKP), which includes 69 clinical registries across different medical specialties (http://www.rkkp.dk/in-english). Patient baseline characteristics, preoperative, operative and postoperative management data is collected and prospectively reported to the database. Reporting to the DCRES is mandatory and the completeness and the quality of data is closely monitored.

The data are initially recorded by the treating surgeon and reported to the DCRS by the surgical departments. The DCRES is linked with other national registers, such as The Danish Transfusion Database, Danish National Database of Reimbursed Prescriptions, The Civil Registration System and The Danish National Patient Registry (DNPR). DNPR provides, among others, information about personal civil registration number, admission and discharge date for all hospitalizations in both private and public hospitals and outpatient speciality clinics in Denmark, including ICD-10 based diagnoses and NOMESCO based codes of surgical procedures [12]. This information is used to ensure the completeness and quality of the data.

The exact date of a patient's death is known through linkage to the patient's civil registration number in the Danish Civil Registration System [13]. All data for this study were collected from the DCRES database.

2.3. Definitions and variables

Predictor variables were chosen based on current knowledge of the prognostic factors for PPU mortality [4,5,14,15]. Creatinine and albumin levels were not included, as data are not available in the database.

The following baseline data were collected; age, gender, height, weight, body mass index (BMI), American Society of Anesthesiologist (ASA) physical status classification, comorbidities (the presence of one or more coexisting illnesses up to five years prior to admission to hospital, including chronic obstructive pulmonary disease (COPD), heart disease, malignant disease or acquired immune deficiency syndrome, cirrhosis or diabetes mellitus). Data were also collected on redeemed prescription for COPD or diabetes mellitus, use of non-steroidal anti-inflammatory drugs (NSAID) steroids, tobacco, alcohol abuse ($>$ 36 g alcohol/day for males and $>$ 24 g alcohol/day for females), surgical delay (time from hospital admission to surgery), shock on admission to the hospital (systolic blood pressure $<$ 100 mmHg together with hart rate $>$ 100) and ulcer location (stomach, duodenum, gastro-duodenum).

2.4. Outcome measures

The primary outcome measure was postoperative 30-day mortality.

2.5. Statistical analysis

The main hypothesis was: H^a: the 30-day mortality risk following operation is lower for laparoscopic surgery than for open surgery. The hypothesis was tested by comparing a group of laparoscopic patients to a group of matched controls receiving open surgery.

A propensity score matching approach was used to identify controls resembling patients receiving laparoscopic treatment. Propensity scores are calculated using a random forest algorithm and transformed into the log of model predicted odds [16,17]. Controls are matched using a nearest-neighbor algorithm with replacement. The same patient can appear as a control for several different cases and is weighted accordingly. A caliper threshold of 0.1 is used to ensure that only neighbors within a 0.1 distance (in the log of odds scale) are matched. The psmatch2 (E. Leuven and B. Sianesi. (2003), PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing) package for Stata 14 was used for the matching. All calculations were performed in Stata 14 and R 3.6.0. Variables which after propensity score matching and weighting are still unbalanced by $p < 0.1$ are introduced as control variables. A variable recording surgical complications is also used as a control variable, but not as a propensity score matching factor because it functions as a mediator and not as a confounder. Surgical complications were defined as a postoperative complication requiring surgical or radiological intervention, such as reperforation, wound dehiscence, drainage of intraabdominal abscess and another intraabdominal reoperation.

Cox proportional hazards regression model was used to compare the mortality of cases and controls. The proportional hazards model was preferred as it involves no assumptions of baseline hazards, only of the proportionality of hazards over time. Postoperative mortality hazard rates can be time dependent, which could lead to a violation of the assumption of constant rates which mark the alternative Poisson model. The Kaplan-Meier survival function was plotted as a visual representation of data.

Laparoscopy patients were compared to the general group of possible controls receiving open surgery, and to the subsample of matched and weighted controls. X^2 statistics and Wilcoxon rank sum tests were used for inferential comparisons. N and percentages were reported for categorical variables; mean and standard deviations were reported for numerical variables.

2.6. Missing data

Additional categories were added containing observations with missing data for each categorical variable with missing observations. Numerical variables with missing data were first recoded into ordinal variables and additional missing category was added. The random forest algorithm for propensity score estimation took into account the missing data categories.

3. Results

A total of 1453 patients were treated surgically in Denmark for PPU from September (1st) 2011 to December (31st) 2015. 36 patients with missing data for the type of treatment were excluded from the study. An additional 31 patients were excluded due to missing date of death. 367 patients who laparoscopic operation followed by open surgery were excluded from the study. Six patients were excluded because of inaccurate recording of the time of death. Five patients with an ASA score of 5 were excluded from the open surgery group, since there were no ASA scores of 5 observed in the laparoscopy group. The total study population comprised 1008 patients, 507 who were treated laparoscopically and 501 who were treated by open surgery. Because of the 0.1 caliper threshold for propensity scores, the final matching analysis sample had 504 in the laparoscopy group and 504 weighted

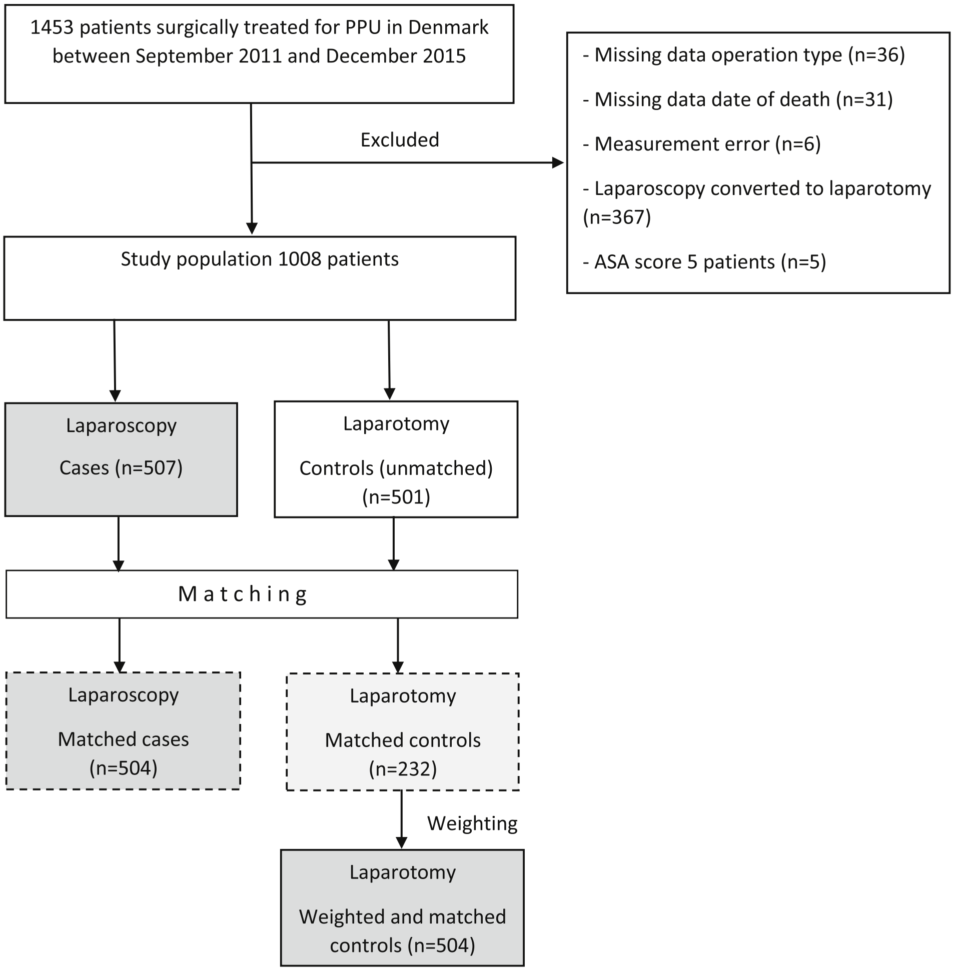


Fig. 1. Study sample flowchart.

observations derived from 232 unique observations in the open surgery group. (Fig. 1).

Before matching, the group of open surgery patients diverged on several important and possibly confounding variables. Tables 1a and 1b shows significantly higher mean age, higher ASA scores, different weight and BMI distributions, different surgery delay time distribution, a higher proportion of patients in hemodynamic shock, different smoking habits, higher prevalence rates of cardiovascular diseases, cirrhosis and malignant diseases in the group of unmatched controls compared to laparoscopy group. After matching and weighting a subset of controls, statistically significant differences were observed only for surgery delay time (Table 1b). Table 2 shows a much higher rate of complications in the laparotomy group. This was balanced after matching. Complications were not included as a matching variable since they occurred after treatment selection.

The unadjusted 30-day mortality was significantly lower for patients receiving the laparoscopic surgery compared to the open surgery (HR = 0.48, 95% CI: 0.36–0.65). After matching and weighting controls, in order to reduce confounding and minimize selection bias, the difference in mortality was reduced and was not significant (HR = 0.88, 95% CI: 0.63–1.23). After controlling further for surgery delay, COPD prescription drug use, NSAID prescription drugs and complications during the procedure the estimated mortality rate was similar in the laparoscopy group and the matched and weighted laparotomy controls (HR = 0.82, 95% CI: 0.59–1.15) (Fig. 2). The 30-day mortality rate was 13.1% (66 out of 504 patients) for laparoscopy and

Table 1a
Baseline characteristics before and after matching – continuous variables.

Continuous measures	Before matching					After matching				
	Laparoscopy (n = 507)		Open surgery - all possible (n = 501)			Laparoscopy (n = 504)		Open surgery - matched and weighted (n = 504)		
	Mean	SD	Mean	SD	p-value (Wilcox.)	Mean	SD	Mean	SD	p-value (Wilcox.)
Age	64.3	18.0	70.7	14.5	0.000	64.5	17.9	66.2	16.3	0.314
ASA score	2.2	0.9	2.6	0.9	0.000	2.2	0.9	2.2	0.9	0.090
Height (cm)	170.5	9.3	169.5	10.1	0.104	170.5	9.3	171.3	10.2	0.412
Weight (kg)	70.9	18.5	70.1	18.3	0.486	70.9	18.6	69.8	15.5	0.796
Body Mass Index	24.3	5.3	24.2	5.2	0.882	24.3	5.3	23.7	4.4	0.389
Hours from registration to operation	25.0	203.0	32.5	132.7	0.017	25.0	203.6	18.3	80.8	0.484

Table 1b
Baseline characteristics before and after matching – categorical variables.

	Before matching					After matching				
	Laparoscopy		Open surgery - all possible			Laparoscopy		Open surgery - matched and weighted		
	n	%	n	%	p-value (χ^2)	n	%	n	%	p-value (χ^2)
Categorical measures	507	100	501	100	0.850	504	100	504	100	
Gender										
Female	253	49.9	249	49.7		251	49.8	231	45.8	
Male	254	50.1	252	50.3	0.949	253	50.2	273	54.2	0.207
Hemodynamically instable patient										
No	472	93.1	403	80.4		470	93.3	465	92.3	
Yes	33	6.5	95	19.0		32	6.3	37	7.3	
Missing	2	0.4	3	0.6	0.000	2	0.4	2	0.4	0.823
Alcohol abuse										
No	426	84.0	403	80.4		424	84.1	425	84.3	
Yes	66	13.0	79	15.8		66	13.1	65	12.9	
Missing	15	3.0	19	3.8	0.327	14	2.8	14	2.8	0.996
Smoking										
Never	137	27.0	152	30.3		137	27.2	124	24.6	
Ex-smoker	64	12.6	95	19.0		64	12.7	57	11.3	
Yes	275	54.2	224	44.7		273	54.2	295	58.5	
Missing	31	6.1	30	6.0	0.007	30	6.0	28	5.6	0.578
Diagnoses										
Diabetes	446	88.0	432	86.2	0.410	445	88.3	457	90.7	0.218
COPD	391	77.1	376	75.0	0.441	389	77.2	406	80.6	0.190
Cardiovascular disease	344	67.9	296	59.1	0.004	341	67.7	334	66.3	0.639
Liver cirrhosis	499	98.4	482	96.2	0.029	496	98.4	500	99.2	0.245
Active malign disease	465	91.7	431	86.0	0.004	462	91.7	457	90.7	0.579
Prescription drugs										
Antidiabetics	455	89.7	444	88.6	0.567	453	89.9	461	91.5	0.386
COPD drugs	400	78.9	392	78.2	0.801	398	79.0	419	83.1	0.091
Steroids	459	90.5	440	87.8	0.166	456	90.5	454	90.1	0.832
NSAID	362	71.4	377	75.2	0.167	359	71.2	385	76.4	0.063
Location of perforation										
Stomach	266	52.5	273	54.5		265	52.6	258	51.2	
Duodenum	201	39.6	200	39.9		201	39.9	218	43.3	
Gastro-duodenum	33	6.5	16	3.2		32	6.3	20	4.0	
Missing	7	1.4	12	2.4	0.064	6	1.2	8	1.6	0.279

Table 2
Distribution of surgical complications.

Surgical complications	Laparotomy		Laparoscopy		Total	
	n	%	n	%	n	%
No complications	376	75.1	444	87.6	820	81.4
Complications	101	20.2	54	10.7	155	15.4
Missing data	24	4.8	9	1.8	33	3.3
Total	501		507		1008	

14.7% (74 out of 504 patients) for the matched controls in the open surgery group. This difference is not significant (p = 0.466). Complications were present in 11.6% of procedures among matched controls and 10.5% in the laparoscopy group. Data was missing for 4.8% among matched controls and 1.6% in the laparoscopy group. The results are robust after adjusting for these possibly mediating mechanisms occurring during the procedure.

4. Discussion

In the present study we demonstrate that laparoscopic treatment for PPU results in a similar adjusted 30-day mortality as PPU treated with open surgery.

Laparoscopic surgery is increasingly being used as the preferred approach for many abdominal surgical emergencies including PPU [8]. Our data supports these observations as we noticed a stable rise in the relative number of laparoscopic operations in our study population, in period from 2011 to 2015 (Fig. 3).

Laparoscopy was less frequently employed in academic institutions compared non-academic institutions with OR 0.55 (95% CI: 0.42–0.71) (Table 3). In two academic university hospitals, surgeons used laparotomy alone as a preferred surgical approach. Possible explanations for this could be a different interpretation of role of laparoscopy in the treatment of patients with PPU or in a definition of a university hospital in Denmark. Three-fifths of the public hospitals in Denmark are registered as university hospitals, mainly because The Faculty of Health and Medical Sciences at the University of Copenhagen, which has collaboration with all hospitals in the Zealand region, makes them part of Copenhagen University Hospital.

We compared open surgery versus laparoscopy in hospitals with 10 and fewer procedures per year to hospitals with more than 10 procedures per year. In hospitals with a larger volume of surgeries, the laparoscopic approach was more common suggesting that the more familiar surgeons are with laparoscopic approach, the more likely they will use it in acute setting (Table 4).

Four randomized controlled trials (RCT) and a several systemic reviews and meta-analyses have examined laparoscopic treatment of PPU [9,18–22]. A 2013 Cochrane review of three RCTs reported no statistically significant difference in mortality between laparoscopic surgery and open surgery. Since 2013, three additional randomized studies have been published. One was retracted, and another had significant methodological limitations, leaving only one study comprising 119 patients; 58 in the laparoscopic and 61 in the open repair group. In a 2016 meta-analysis of five RCTs, mortality rates in the laparoscopic and open surgery groups were similar [22].

Møller at al reported greater age, comorbidity, ASA class III and IV, use of NSAID and steroids, delayed surgery > 24 h, shock, abnormal levels of serum albumin, creatinine and pH were associated with

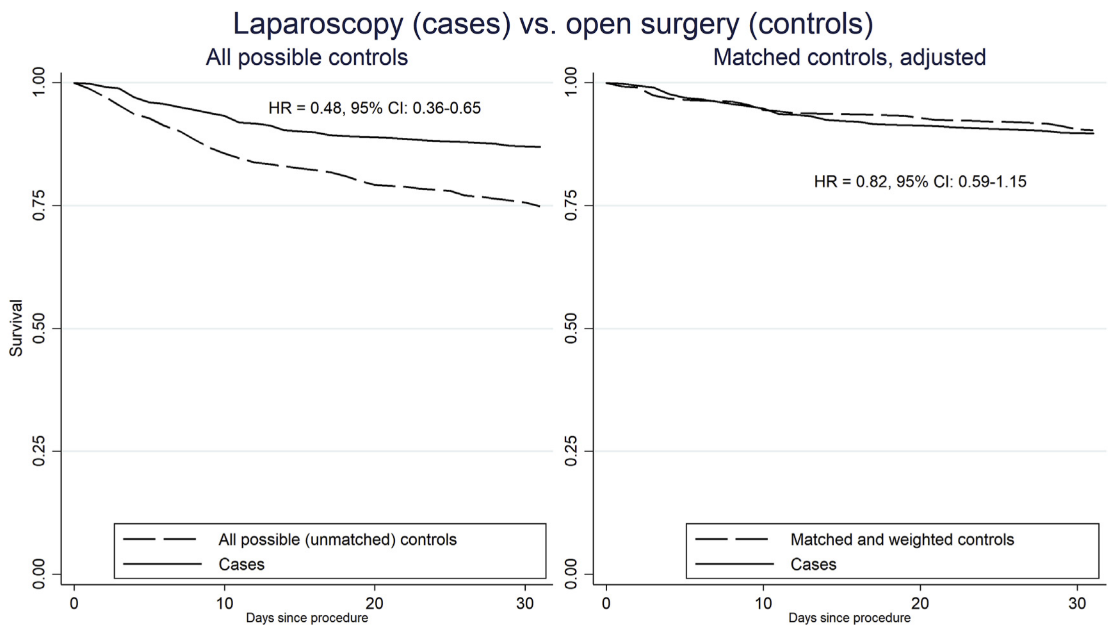


Fig. 2. Mortality in patients with PPU comparing laparoscopy vs. open surgery, before and after matching and adjusting for the differences of known confounders.

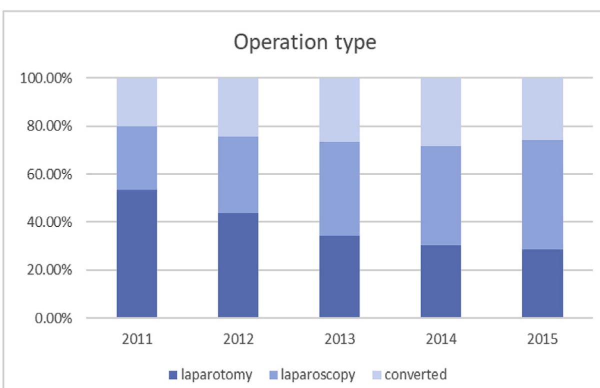


Fig. 3. Distribution of surgical approach for treatment of PPU in our study.

Table 3
Distribution of surgical approach in Academic vs. Non-academic Institutions.

Academic Institution	Laparotomy		Laparoscopy		Total	
	n	%	n	%	n	%
Yes	360	54.96	295	45.04	655	100
No	141	39.94	212	60.06	353	100
	501		507		1008	

Table 4
Distribution of surgical approach in Low-volume vs. High-volume Institutions.

Number of operations for PPU per institution	Laparotomy		Laparoscopy		Total	
	n	%	n	%	n	%
≤10 operations per year	210	60	140	40	350	100
> 10 operations per year	291	44.22	367	55.78	658	100
Total	501		507		1008	

mortality [4]. Low BMI and surgical delay after admission to hospital also have been recognized as independent prognostics factors for mortality [14,15]. Some of these factors are incorporated into scoring systems used to predict outcomes in PPU patients. The most commonly used are Boey score and ASA classification [23,24]. The later employs the PULP score with similar or slightly better accuracy [25]. Outcome scoring systems have not identified the type of surgery as a factor that predicts mortality.

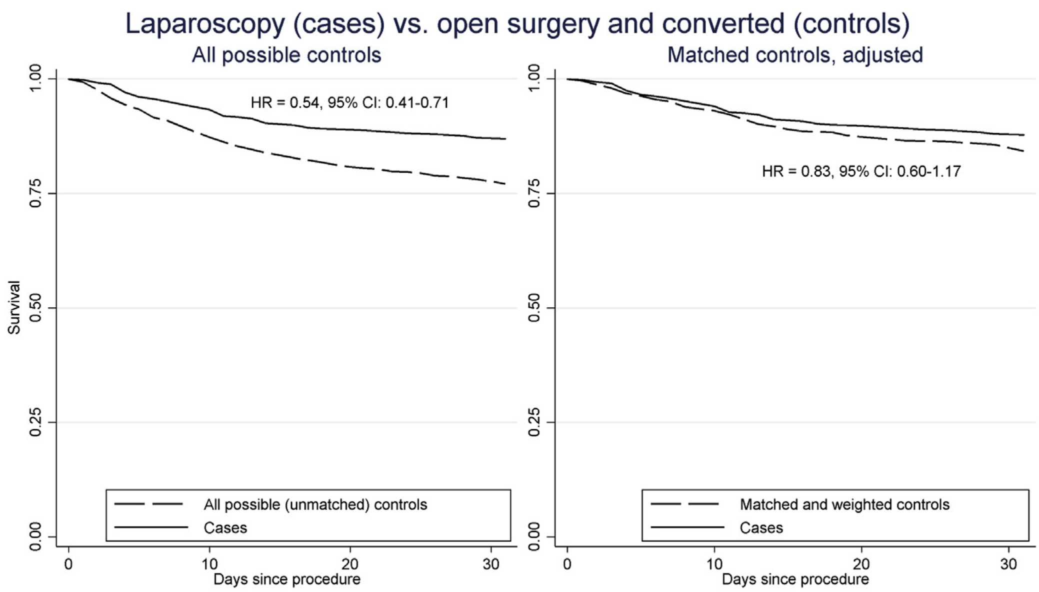
Our unadjusted results showed a significant difference in mortality in patients with PPU treated with laparotomy compared to laparoscopy. This difference, however, disappeared after patients in these two groups were matched using known mortality risk factors and the influence of confounding factors were minimized (Fig. 2).

Wilhelmsen at al reported a lower risk of re-operation in patients undergoing laparoscopy surgery compared to open surgery or those who underwent open surgery following laparoscopy [26]. In their study, 90-day mortality was higher in patients who had re-operation, though not statistically significant. The study included the same population in the that we used in our study. This raises the question if there is a potential benefit of laparoscopic surgery in terms of 90-day mortality and if the rate of surgical complications is related to the surgical approach This question should be answered in future randomized controlled trials.

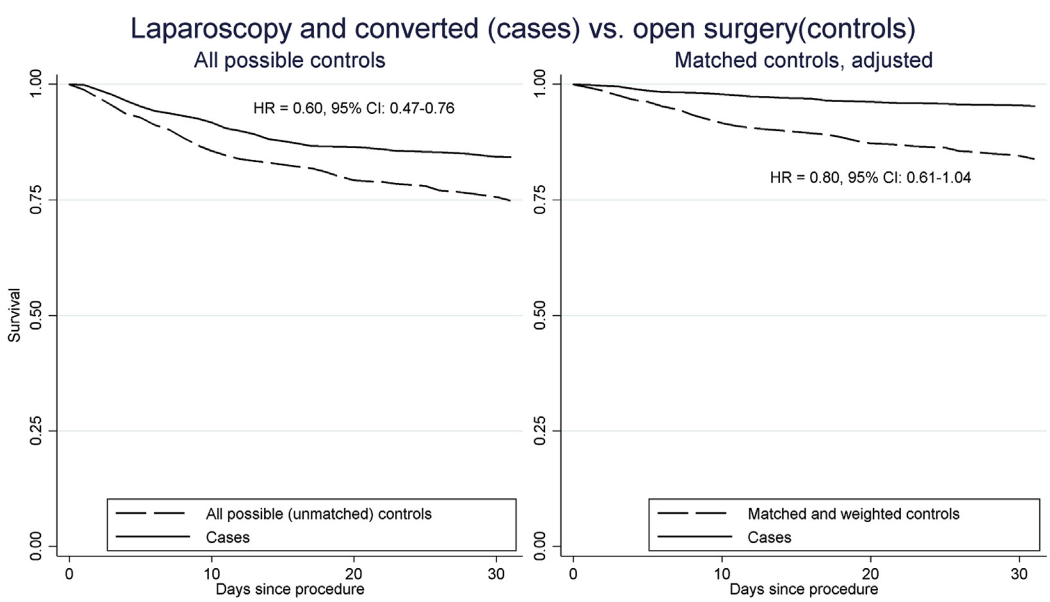
We chose to use a per-protocol analysis and to eliminate patients who underwent laparoscopic surgery followed by open surgery. We know from the previous research [26] that patients who have laparoscopy followed by open surgery have a higher risk of complications comparing to laparoscopy. We felt that per-protocol analysis would provide the optimal way to investigate the potential association between the surgical approach and outcome. Aware of risk for bias inherent in the chosen methodology, we conducted additional sensitivity analyses (Fig. 4a, b and 4c), where laparoscopy followed by surgery were included both on intention-to-treat and as-treated basis. The results of the sensitivity analyses are consistent with results from per-protocol analysis supporting the inference that there is no association between short term mortality and surgical approach.

We contemplated using postoperative complications as a matching factor in our analysis. It appears that postoperative surgical complications are a complex mortality factor that is heavily associated to other known preoperative mortality factors. There was a higher risk of complications in the laparotomy group compared to laparoscopy before matching, which was equilibrized after matching. This indicates that the preoperative mortality factors not only predict mortality but also the risk of postoperative complications.

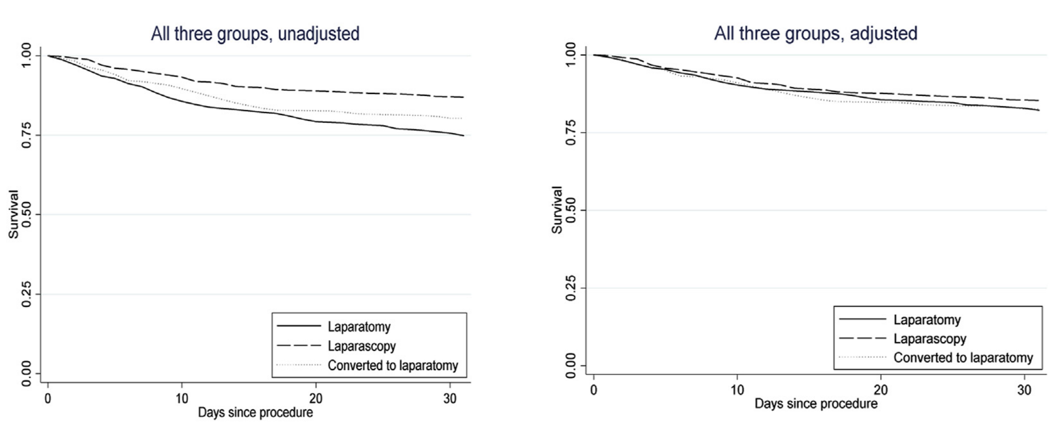
We applied matching with replacements, with the possibility of



a



b



c

Fig. 4. a) Sensitivity analysis of converted laparoscopic operations: As-treated Analysis. (b) Sensitivity analysis of converted laparoscopic operations: Intention-to-treat Analysis. (c) The overall survival functions before any matching: Crude and adjusted survival functions.

matching one control to several cases. We chose to use this approach because we had less data from controls compared to cases. The simpler replacement weights that we used allowed us to create a control sample that could be evaluated and compared to the laparoscopic patients in a simple and transparent manner, similar to a randomized control group [27].

Limitations of this study are the statistical analysis (propensity score) and the observational study design. Mortality was adjusted for most of the currently known mortality predictors. Other known mortality predictors such as low albumin and high creatinine levels, as well as other potential factors such as postoperative complications or duration of hospitalization, that could influence mortality, were not included in the analysis.

External validity of the study is ensured by using appropriate statistical analysis to strengthen internal validity and by replicating results from the randomized controlled trials based on different study populations from China and Netherlands.

5. Conclusion

In conclusion, the present study demonstrates that laparoscopic surgery in patients with PPU has a similar 30-day mortality to open surgery when adjusted for known mortality risk factors. More well powered randomized clinical trials are needed to investigate the role of laparoscopic surgery in treatment of patients with PPU.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

The data from The Danish Clinical Registries (RKKP) are available on request, for research purposes to any Danish medical professional (email: fagligkvalitet@rkkp.dk). The data sharing is regulated by The Data Protection Act and The General Data Protection Regulation (GDPR) and under supervision of The Danish Data Protection Agency (email: dt@datatilsynet.dk).

Ethical approval

The study was approved by the Danish Data Protection Agency through the Data Inspectorate for Clinical Quality Databases approved by Statens Serum Institut, cf. 2012-58-0023.

Sources of funding

The study was financially supported by Knud og Edith Eriksens Mindefond.https://www.keemindefond.dk/

Research registration number

1. Name of the registry: https://www.researchregistry.com
2. Unique Identifying number or registration ID: researchregistry4991
3. Hyperlink to the registration (must be publicly accessible): https://www.researchregistry.com/register-now#home/registrationdetails/5d1ddfe72ab6b500125638a8/

Guarantor

Sergej Zogovic.

CRediT authorship contribution statement

Sergej Zogovic: Conceptualization, Writing - review & editing, Formal analysis. **Anders Bo Bojesen:** Writing - review & editing, Formal analysis. **Shadi Andos:** Writing - review & editing. **Frank Viborg Mortensen:** Writing - review & editing, Conceptualization.

Declaration of competing interest

Authors have no conflicts of interest to disclose.

Acknowledgments

This study would not be possible without assistance from the Danish Clinical Register of Emergency Surgery, which provided the data necessary to conduct the study.

We want to thank Knud og Edith Eriksens Mindefond for the financial support of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.10.017.

References

[1] J.Y. Lau, J. Sung, C. Hill, C. Henderson, C.W. Howden, D.C. Metz, Systemic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality, Digestion 84 (2011) 102–113, https://doi.org/10.1159/000323958.

[2] K. Thorsen, J.A. Søreide, J.T. Kvaløy, T. Glomsaker, K. Søreide, Epidemiology of perforated peptic ulcer: age- and gender-adjusted analysis of incidence and mortality, World J. Gastroenterol. 19 (2013) 347–354, https://doi.org/10.3748/wjg.v19.i3.347.

[3] Y.R. Wang, J.E. Richter, D.T. Dempsey, Trends and outcomes of hospitalizations for peptic ulcer disease in the United States, 1993 to 2006, Ann. Surg. 251 (2010) 51–58, https://doi.org/10.1097/SLA.0b013e3181b975b8.

[4] M.H. Møller, S. Adamsen, R.W. Thomsen, A.M. Møller, Preoperative prognostic factors for mortality in peptic ulcer perforation: a systemic review, Scand. J. Gastroenterol. 45 (2010) 785–805, https://doi.org/10.3109/00365521003783320.

[5] K. Thorsen, J.A. Søreide, K. Søreide, What is the best predictor of mortality in perforated peptic ulcer disease? A population-based, multivariable regression analysis including three clinical scoring systems, J. Gastrointest. Surg. 18 (2014) 1261–1268, https://doi.org/10.1007/s11605-014-2485-5.

[6] K. Thorsen, J.A. Søreide, K. Søreide, Scoring systems for outcome prediction in patients with perforated peptic ulcer, Scand. J. Trauma Resusc. Emerg. Med. 21 (2013) 25, https://doi.org/10.1186/1757-7241-21-25.

[7] L.K. Nathanson, D.W. Easter, A. Cuschieri, Laparoscopic repair/peritoneal toilet of perforated duodenal ulcer, Surg. Endosc. 4 (1990) 232–233.

[8] K. Thorsen, T.B. Glomsaker, A. von Meer, K. Søreide, J.A. Søreide, Trends in diagnosis and surgical management of patients with perforated peptic ulcer, J. Gastrointest. Surg. 15 (2011) 1329–1335, https://doi.org/10.1007/s11605-011-1482-1.

[9] A. Sanabria, M.I. Villegas, C.H. Morales Uribe, Laparoscopic repair for perorated peptic ulcer disease, Cochrane Database Syst. Rev. (2013), https://doi.org/10.1002/14651858.CD004778.pub3 CD004778.

[10] S. Di Saverio, M. Bassi, N. Smerieri, M. Masetti, F. Ferrara, C. Fabbri, L. Ansaloni, S. Ghersi, M. Serenari, F. Coccolini, N. Naidoo, M. Sartelli, G. Tugnoli, F. Catena, V. Cennamo, E. Jovine, Diagnosis and treatment of perforated or bleeding peptic ulcers: 2013 WSES position paper, World J. Emerg. Surg. 9 (2014) 45, https://doi.org/10.1186/1749-7922-9-45.

[11] R.A. Agha, M.R. Borrelli, M. Vella-Baldacchino, R. Thavayogan, D.P. Orgill, STROCSS Group, The STROCSS statement: strengthening the reporting of cohort studies in surgery, Int. J. Surg. 46 (2017) 198–202, https://doi.org/10.1016/j.ijsu.2017.08.586.

[12] M. Schmidt, S.A.J. Schmidt, J.L. Sandegaard, V. Ehrenstein, L. Pedersen, H.T. Sørensen, The Danish National Patient Registry: a review of content, data quality, and research potential, Clin. Epidemiol. 7 (2015) 449–490, https://doi.org/10.2147/CLEP.S91125.

[13] C.B. Pedersen, The Danish civil registration system, Scand. J. Public Health 39 (2011) 22–25, https://doi.org/10.1177/1403494810387965.

[14] D.L. Buck, M. Vester-Andersen, M.H. Møller, Surgical delay is a critical determinant of survival in perforated peptic ulcer, Br. J. Surg. 100 (2013) 1045–1049, https://doi.org/10.1002/bjs.9271.

[15] D.L. Buck, M.H. Møller, Influence of body mass index on mortality after surgery for perforated peptic ulcer, Br. J. Surg. 101 (2014) 993–999, https://doi.org/10.1002/bjs.9529.

[16] D.B. Rubin, Using propensity score to help design observational studies: application to the tobacco litigation, Health Serv. Outcomes Res. Methodol. 2 (2001) 169–188.

[17] A. Liaw, M. Wiener, Classification and regression by random forest, R. News 2 (2002) 18–22.

[18] W.Y. Lau, K.L. Leung, K.H. Kwong, I.C. Davey, C. Robertson, J.J.W. Dawson, S.C.S. Chung, A.K.C. Li, A randomized study comparing laparoscopic versus open

repair of perforated peptic ulcer using suture or sutureless technique, Ann. Surg. 224 (1996) 131–138, https://doi.org/10.1097/00000658-199608000-00004.

[19] W.T. Siu, H.T. Leong, B.K.B. Law, C.H. Chau, A.C.N. Li, K.H. Fung, Y.P. Tai, M.K.W. Li, Laparoscopic repair for perforated peptic ulcer. A randomized controlled trial, Ann. Surg. 235 (2002) 313–319, https://doi.org/10.1097/00000658-200203000-00001.

[20] M.J.O.E. Bertleff, J.A. Halm, W.A. Bemelman, A.C. van der Ham, E. van der Harst, H.I. Oei, J.F. Smulders, E.W. Steyerberg, J.F. Lange, Randomized clinical trial of laparoscopic versus open repair of the perforated peptic ulcer: the LAMA trial, World J. Surg. 33 (2009) 1368–1373, https://doi.org/10.1007/s00268-009-0054-y.

[21] B. Ge, M. Wu, Q. Chen, Q. Chen, R. Lin, L. Liu, Q. Huang, A prospective randomized controlled trial of laparoscopic repair versus open repair for perforated peptic ulcers, Surgery 159 (2016) 451–458, https://doi.org/10.1016/j.surg.2015.07.021.

[22] S. Tan, G. Wu, Q. Zhuang, Q. Xi, Q. Meng, Y. Jiang, Y. Han, C. Yu, Z. Yu, N. Li, Laparoscopic versus open repair for perforated peptic ulcer: a meta analysis of randomized controlled trials, Int. J. Surg. 33 (2016) 124–132, https://doi.org/10.1016/j.ijsu.2016.07.077.

[23] J. Boey, S.K.Y. Choi, A. Poon, T.T. Alagaratnam, Risk stratification in perforated duodenal ulcers, Ann. Surg. 205 (1987) 22–26, https://doi.org/10.1097/00000658-198701000-00005.

[24] J. Fitz-Henry, The ASA classification and peri-operative risk, Ann. R. Coll. Surg. Engl. 93 (2011) 185–187, https://doi.org/10.1308/rcsann.2011.93.3.185a.

[25] M.H. Møller, M.C. Engebjerg, S. Adamsen, J. Bendix, R.W. Thomsen, The peptic ulcer perforation (PULP) score: a predictor of mortality following peptic ulcer perforation. A cohort study, Acta Anaesthesiol. Scand. 56 (2012) 655–662, https://doi.org/10.1111/j.1399-6576.2011.02609.x.

[26] M. Wilhelmsen, M.H. Møller, S. Rosenstock, Surgical complications after open and laparoscopic surgery for perforated peptic ulcer in a nationwide cohort, Br. J. Surg. 102 (2015) 382–387, https://doi.org/10.1002/bjs.9753.

[27] S. Deb, P.C. Austin, J.V. Tu, D.T. Ko, C.D. Mazer, A. Kiss, S.E. Fremes, A review of propensity-score methods and their use in cardiovascular research, Can. J. Cardiol. 32 (2016) 259–265, https://doi.org/10.1016/j.cjca.2015.05.015.