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Original Contribution

Sex dependence of postoperative pulmonary complications – A post hoc unmatched and matched analysis of LAS VEGAS

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HIGHLIGHTS

- Sex is not associated to the incidence of postoperative pulmonary complications (PPCs) in a general surgical population.
- Matched for similar preoperative PPC risk and type of surgery, no relevant difference in PPC incidence was found between female and male patients.
- New invasive ventilation did occur less often in females in the unmatched analysis, but not in the matched analysis.
- Hospital mortality and length of stay was similar between the sexes.

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[3] for full list of SWARM contributors please see www.ukswarm.com
[4] PROtective VEntilation Network (www.provenet.eu)

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ABSTRACT

Study objective: Male sex has inconsistently been associated with the development of postoperative pulmonary complications (PPCs). These studies were different in size, design, population and preoperative risk. We reanalysed the database of 'Local ASsessment of Ventilatory management during General Anaesthesia for Surgery study' (LAS VEGAS) to evaluate differences between females and males with respect to PPCs.

Design, setting and patients: Post hoc unmatched and matched analysis of LAS VEGAS, an international observational study in patients undergoing intraoperative ventilation under general anaesthesia for surgery in 146 hospitals across 29 countries. The primary endpoint was a composite of PPCs in the first 5 postoperative days. Individual PPCs, hospital length of stay and mortality were secondary endpoints. Propensity score matching was used to create a similar cohort regarding type of surgery and epidemiological factors with a known association with development of PPCs.

Main results: The unmatched cohort consisted of 9697 patients; 5342 (55.1%) females and 4355 (44.9%) males. The matched cohort consisted of 6154 patients; 3077 (50.0%) females and 3077 (50.0%) males. The incidence in PPCs was neither significant between females and males in the unmatched cohort (10.0 vs 10.7%; odds ratio (OR) 0.93 [0.81–1.06]; $P = 0.255$), nor in the matched cohort (10.5 vs 10.0%; OR 1.05 [0.89–1.25]; $P = 0.556$). New invasive ventilation occurred less often in females in the unmatched cohort. Hospital length of stay and mortality were similar between females and males in both cohorts.

Conclusions: In this conveniently–sized worldwide cohort of patients receiving intraoperative ventilation under general anaesthesia for surgery, the PPC incidence was not significantly different between sexes.

Registration: LAS VEGAS was registered at clinicaltrial.gov (study identifier NCT01601223).

1. Introduction

Sex is a patient characteristic that is often implemented in risk classification tools in healthcare practices [1–3]. Sex differences in medicine refer to the biological and physiological differences between females and males that may impact how they respond to medical treatments, therapies, or interventions [4,5]. Understanding these differences could help tailoring treatments to patients' unique needs and potentially optimize outcomes [6,7]. In anaesthesia, many inequalities have been reported between females and males [8].

Postoperative pulmonary complications (PPCs), even when mild, are associated with increased length of hospital stay and mortality [9,10]. An association between male sex and PPCs has been mentioned in univariable [11,12] and multivariable regression [13,14], while other studies did not detect a higher incidence of PPCs in males [15–17]. In addition, it's possible PPC composites do not differ between sexes, but individual PPCs could. A better understanding of sex differences in PPCs could possibly lead to improved risk classification tools, use of perioperative lung protective strategies and early recognition and treatment of PPCs.

We hypothesized sex is associated with the development of PPCs. However this is due to a difference in preoperative risk, rather than to sex itself. To test this hypothesis, we used the database of a conveniently–sized study of intraoperative ventilation and PPCs, named 'Local Assessment of VEntilatory management during General Anaesthesia for Surgery' (LAS VEGAS) [18,19]. To evaluate the role of preoperative risk, we used propensity score matching to create similar groups regarding type of surgery and epidemiological factors with a known association to development of PPCs.

2. Materials and methods

Post hoc unmatched and matched analysis of LAS VEGAS [18,19], a worldwide, prospective 1–week observational study describing intraoperative ventilation management and postoperative complications in the first five postoperative days in patients undergoing surgery in 146 centres in 29 countries. Patients were enrolled between 14 January and 4 March 2013. The study protocol of LAS VEGAS was first approved on 22 August 2012 by the ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands (W12_190#12.17.0227, chairperson Prof. M.P.M. Burger). If needed, approval was obtained from the institutional review board in other centres, and depending on national or regional legislation written informed consent was obtained from each individual patient. LAS VEGAS was registered at clinicaltrials.gov (study identifier NCT01601223). The statistical analysis plan for the current analysis was predefined and approved by the LAS VEGAS steering committee before data extraction. This report followed the guidelines and recommendations of the 'STrengthening the Reporting of OBservational studies in Epidemiology' (STROBE) statement (see **Supplement Table 1** in the supplementary material).

2.1. Inclusion and exclusion criteria

LAS VEGAS enrolled consecutive patients receiving invasive ventilation during general anaesthesia for surgery during a predefined calendar week. Exclusion criteria of LAS VEGAS were: (1) age < 18 years, (2) obstetric procedures, (3) procedures with cardiopulmonary bypass, and (4) surgical procedures that were not performed in the operating room. All patients in the original LAS VEGAS cohort were screened for eligibility for the current analysis. We excluded patients having received mechanical ventilation in the preceding month, and patients receiving one lung ventilation for thoracic surgery. We also excluded patients with an incomplete follow up with regard to PPCs.

2.2. Data recording and processing

The following data were collected in LAS VEGAS—baseline characteristics and demographic data, including but not limited to sex, age, body weight and height, American Society of Anaesthesiologists (ASA) physical score, functional status, comorbidities, anaesthesia characteristics and surgical characteristics; risk for PPCs, by means of the 'Assess Respiratory Risk in Surgical Patients in Catalonia' (ARISCAT) risk score for PPCs [13]; occurrence of predefined PPCs in the first 5 postoperative days; and date of hospital discharge and life–status at hospital discharge or day 28.

2.3. Endpoints

The primary endpoint was the occurrence of one or more PPCs in the first 5 postoperative days in the unmatched analysis—a composite endpoint including six individual PPCs, all as defined in Section 2.4 below. The occurrence of one individual PPC was defined as having met the primary endpoint. Secondary endpoints were the incidence of individual PPCs, hospital length of stay (LOS) and hospital mortality.

2.4. Definitions

Sex was defined as sex assigned at birth, comprising a binary variable and as recorded in the medical file of the respective participating center. The composite of PPCs consisted of 1) unplanned supplementary oxygen (oxygen administered due to $PaO_2 < 8$ kPa or $SpO_2 < 90\%$ in room air, but excluding oxygen supplementation given as standard care, e.g. directly after arrival in the postanaesthetic care unit); 2) respiratory failure ($PaO_2 < 8$ kPa or $SpO_2 < 90\%$ despite oxygen therapy, or a need for noninvasive ventilation; 3) unplanned new or prolonged invasive mechanical ventilation (after discharge from the operating room); 4) ARDS (defined according to the Berlin definition of ARDS) [20]; 5) pneumonia (presence of a new or progressive radiographic infiltrate and at least two of three clinical features; fever >38 °C or > 100.4 °F, leucocytosis or leukopenia (white blood cell count >12,000 cells μl^{-3} or < 4000 cells μl^{-3} and purulent secretions), and 6) pneumothorax (air in the pleural space with no vascular bed surrounding the visceral pleura on the chest radiograph).

2.5. Sample size calculation

No sample size calculation was performed for this analysis; the total number of patients included in LAS VEGAS served as the sample size for this analysis. A posthoc power calculation was performed for the primary endpoint.

2.6. Statistical analysis

Continuous variables are presented as medians with interquartile range; categorical variables are expressed in numbers with percentages. Descriptive statistics were used to compare patient demographics and anaesthesia and surgical characteristics.

For all analyses, male patients were used as the reference. Female patients were compared with male patients using an unpaired t–test or Mann–Whitney *U* test for continuous variables. The incidence of PPCs was compared between females and males using a Fisher's exact test. Hospital LOS was assessed using a Fine–Gray analysis considering death before discharge as competing risk. Hospital mortality was compared using a cox shared–frailty model with centre as shared frailty. Among survivors, the risk of hospital discharge was compared using a cox shared–frailty model with centre as shared frailty.

To create the matched cohort, a propensity score matching was performed. For all patients a propensity score was estimated with logistic regression to quantify preoperative risk for developing PPCs. Consequently, females were matched to male patients with a comparable risk for PPCs. Baseline characteristics implemented in the propensity score matching were chosen on clinical relevance, i.e. with a known association with PPCs, but not on the causal pathway between sex and PPCs. Variables included in the ARISCAT risk score were not incorporated in the model again. The propensity score model consisted of: the ARISCAT risk score; type of surgery (excluding sex exclusive procedures); functional status; smoking status at the time of surgery, and presence of chronic comorbidities including chronic obstructive lung disease, liver dysfunction, any neuromuscular disease affecting the respiratory system, metastatic cancer, heart failure, chronic kidney dysfunction and obstructive sleep apnoea. Missing data was imputed using multiple imputation (5 computations, 5 iterations and pooled results, MICE package) if data was considered missing completely at random and not exceeding 5% of all observations. A maximum calliper of 0.15 was used with an additional calliper of 0.15 for the ARISCAT score to ensure similar baseline risk for PPCs. The method of nearest neighbour matching without replacement was applied in a 1:1 ratio. Balance of covariates between groups was assessed using a LOVEplot with standardized mean differences (SMD). Adequate balance between covariates was defined as not exceeding 0.1 SMD.

Three post hoc sensitivity analyses have been performed to evaluate the association between sex and PPCs, consisting of 1) a multiple logistic regression model in the unmatched cohort using the same covariates as implemented in the propensity score model; 2) a multiple logistic regression model in the unmatched cohort with the propensity score as covariate and 3) a generalized linear mixed−effects model in the matched cohort with the matched pairs as random effect.

All analyses were performed using R software 4.2.1. The posthoc power analysis was performed using GPower version 3.1.9.7. A *P*–value <0.05 was considered statistically significant. We applied a Bonferroni correction for the six individual PPCs to address family wise error rate in multiple comparisons, leading to a $P -$ value <0.0083 as the threshold for statistical significance.

3. Results

The original cohort of LAS VEGAS contained 10,520 patients (Fig. 1). Main reasons for excluding patients for the current analysis were recent ventilation and intraoperative one–lung ventilation for thoracic surgery. After exclusion of patients with missing follow up, we were left with 9697 patients, 5342 females and 4355 males. In the unmatched cohort, females were younger, shorter and weighted less than males (Table 1). Females were assigned an ASA score of 1 and 2 more often than males, and females had lower median ARISCAT risk scores. Females smoked less frequently, and had comorbidities less often. Females underwent elective surgeries more often, and duration of surgery was shorter.

The matched cohort contained 6154 patients; 3077 females and 3077 males. In the matched cohort, covariates were well balanced (**Supplement Fig. 1** and Table 1). Specifically, females had a median ARISCAT risk score comparable to males.

3.1. Incidence of PPCs

In the unmatched analysis, the incidence of PPCs in females was similar to males (10.0 vs 10.7%, OR 0.93 [0.81–1.06], $P = 0.255$) (Table 2), females experienced new invasive ventilation less often ($P = 0.008$) In the matched analysis, the incidence of PPCs was also similar between the sexes (10.5 vs 10.0%, OR 1.05 [0.89–1.25], $P = 0.556$) (Table 2). There were also no relevant differences in the individual PPCs between the sexes.

3.2. Hospital LOS and mortality

In the unmatched analysis, females had a shorter median hospital LOS in days. The female hazard ratio for discharge with death as competing risk, and the hazard ratio for discharge among surviving patients was not statistically significant. Hospital mortality was not different between the sexes (Table 3 and Fig. 2). In the matched analysis, surviving females were more likely to get discharged than surviving males. Mortality differences were not statistically significant between females and males (Table 3 and Fig. 3).

3.3. Post hoc power analysis and sensitivity analyses

The three post hoc sensitivity analyses did not change the findings (**Supplement Table 3–5**). We considered a relative risk reduction of 14.4% for PPCs in females clinically relevant, corresponding to an absolute risk reduction of 1.5%. Considering the total PPC incidence in LAS VEGAS of 10.4% [18], with the unmatched cohort sample size of 9697 patients, an α of 0.05, a female to male ratio of 1.23, the post−hoc power analysis showed that we had 90% power to detect this difference.

4. Discussion

The results of this post hoc unmatched and matched analysis of LAS VEGAS can be summarized as follows: (1) in the unmatched analysis, there was no clinically relevant difference in PPC incidence between

females and males, albeit that new invasive ventilation was less often seen in females; (2) in the analysis matched for epidemiological factors with a known association with development of PPCs and type of surgery, the composite and individual incidence of PPCs remained similar between females and males; and (3) there were no major differences in hospital LOS and mortality between the sexes, both in the unmatched and in the matched cohort.

This analysis has several strengths. LAS VEGAS was an international and multicentre study in both low and high income countries, performed in both academic and non – academic hospitals, and in teaching and non – teaching centres, increasing the generalizability of our findings. LAS VEGAS included a large variety of procedures which also helps our understanding of sex differences in outcome of surgery. The large sample size allowed for sophisticated analyses and precise estimation and control for confounding factors. We also conducted multiple sensitivity analyses to evaluate our findings. We used the criteria for PPCs as in the original publication. The statistical analysis plan was predefined and strictly followed, preventing any bias.

The findings of our study challenge what was found in previous investigations [11–14]. Of note, these studies were all different in preoperative risk for PPCs, size, design and patient populations. The studies also used distinct definitions and composites of PPCs. Nevertheless, opposite to what was found in those studies we show no clinically relevant difference in the incidence of PPCs between females and males. In one of those previous studies conducted in Italy, the odds of male patients developing PPCs in multivariable analysis was reported to be nearly three times higher [14]. In two other studies male sex was associated with PPCs in a German population of oral and maxillofacial surgery [11] and in a Korean population undergoing a variety of procedures [12]. These associations were however only found in univariable regression. In the fourth study an association of male sex with PPCs was observed in multivariable analysis in a variety of procedures in Spain [13]. The ARISCAT risk score for PPCs is derived from this study, a limitation was the sample size not being sufficient for all variables that were put into the model. Hence, bootstrap sampling was used as a validation tool and male sex was not present as predictor in >80% of the samples. This did not necessarily mean male sex was not associated to PPCs, as this would need a larger sample to prove. Our analysis suggests PPC risk scores should indeed not include male sex as predictor. We believe that our approach of directly comparing the incidences of PPCs between the sexes in an unmatched analysis, and in matched analysis mitigating the effect of baseline PPC risk and type of surgery, is a better way to investigate associations of sex with this important outcome.

The findings of our study align more with previous investigations, which also found no association of sex with PPCs after various types of surgery [15–17]. It must be recognized that the design of these studies also differed from ours. While we did detect a lower incidence of the individual PPC new invasive ventilation among females in the unmatched analysis, this was not found in the matched analysis, suggesting this could be due to preoperative PPC risk and type of surgery instead of female sex itself.

Prior studies consistently show that females receive more often ventilation with a too high tidal volume (V_T) compared to males, both in critical care settings [21–24] and operating rooms [25–28]. Since

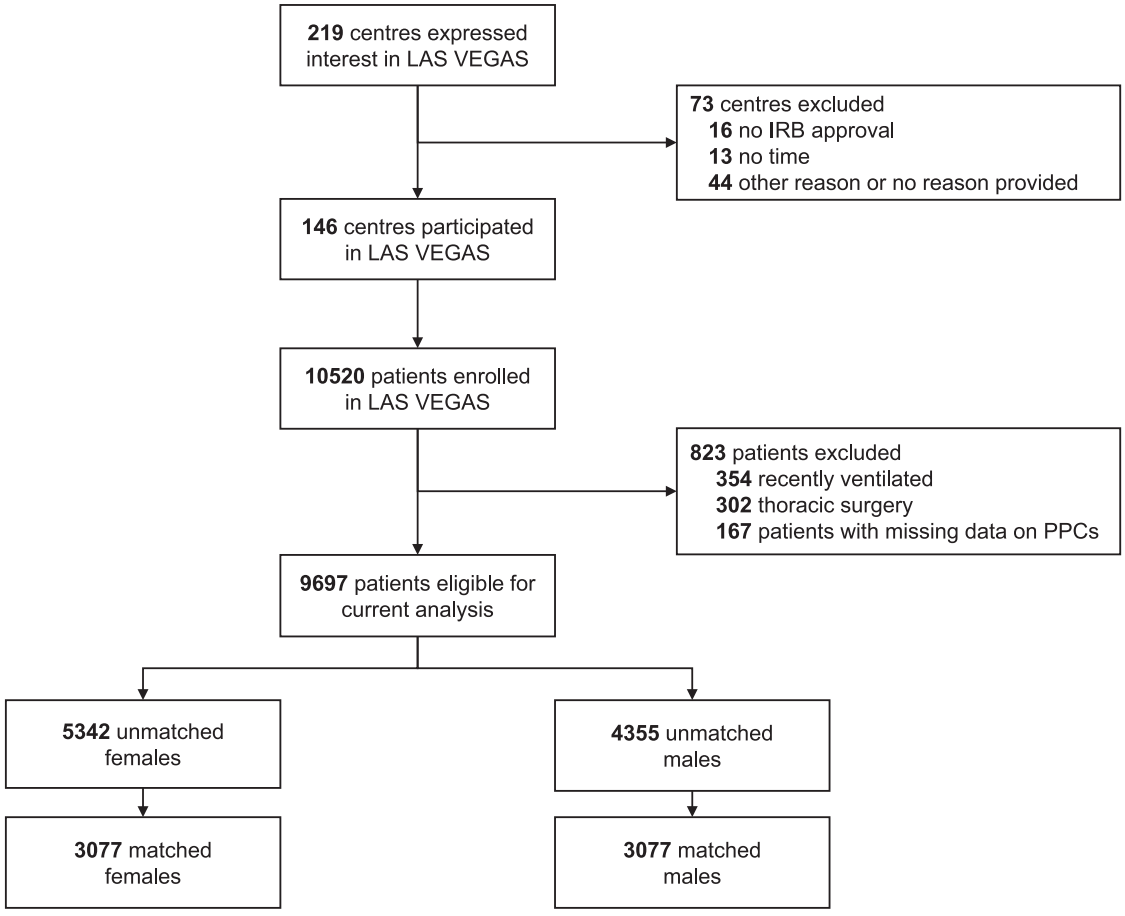


Fig. 1. CONSORT flowchart.

Table 1
Patient characteristics unmatched and matched cohorts.

	unmatched cohort				matched cohort			
	female patients *N* = 5342	male patients *N* = 4355	p	SMD	female patients *N* = 3077	male patients N = 3077	p	SMD
Demographics								
age, years (median [IQR])	52 [39–64]	55 [40–67]	<0.001	0.104	54 [41–66]	55 [39–67]	0.872	0.015
height, cm (median [IQR])	162 [156–168]	174 [168–180]	<0.001	0.214	162 [156–168]	175 [168–180]	<0.001	0.263
weight, kg (median [IQR])	69 [59–80]	80 [70–92]	<0.001	0.436	69 [59–80]	81 [71–93]	<0.001	0.496
BMI, kg/m^2 (median [IQR])	26 [23–30]	27 [24–30]	<0.001	0.009	26 [23–30]	27 [24–30]	<0.001	0.002
ARISCAT risk score (median [IQR])	15 [3–26]	16 [3–27]	0.270	0.035	15 [3–26]	15 [3–26]	0.855	0.002
ARISCAT risk score group, n (%)			<0.001	0.090			0.993	0.003
low, < 26	3766 (73.5)	2909 (69.5)			2242 (72.9)	2239 (72.8)		
intermediate, 26–45	1132 (22.1)	1052 (25.1)			690 (22.4)	694 (22.6)		
high, ≥ 45	224 (4.4)	224 (5.4)			145 (4.7)	144 (4.7)		
ASA group, n (%)			<0.001	0.162			0.071	0.073
ASA 1	1685 (31.6)	1248 (28.7)			858 (27.9)	943 (30.7)		
ASA 2	2668 (50.1)	2018 (46.4)			1522 (49.5)	1422 (46.3)		
ASA 3	897 (16.8)	982 (22.6)			635 (20.7)	645 (21.0)		
ASA 4	73 (1.4)	95 (2.2)			55 (1.8)	61 (2.0)		
ASA 5	4 (0.1)	4 (0.1)			2 (0.1)	1 (0.0)		
Functional status, n (%)			0.213	0.036			0.104	0.055
independent	4953 (92.8)	4000 (91.9)			2792 (90.7)	2836 (92.2)		
partially dependent	324 (6.1)	285 (6.6)			250 (8.1)	206 (6.7)		
totally dependent	63 (1.2)	66 (1.5)			35 (1.1)	35 (1.1)		
Smoker, yes, n (%)	993 (18.6)	1255 (28.8)	<0.001	0.242	687 (22.3)	699 (22.7)	0.737	0.009
Comorbidities, yes, n (%)								
COPD	259 (4.8)	329 (7.6)	<0.001	0.112	198 (6.4)	189 (6.1)	0.674	0.012
heart failure	285 (5.3)	289 (6.6)	0.007	0.055	187 (6.1)	180 (5.8)	0.747	0.010
metastatic cancer	188 (3.5)	200 (4.6)	0.008	0.054	132 (4.3)	126 (4.1)	0.751	0.010
chronic kidney dysfunction	124 (2.3)	183 (4.2)	<0.001	0.106	105 (3.4)	111 (3.6)	0.729	0.011
obstructive sleep apnoea	91 (1.7)	114 (2.6)	0.002	0.063	77 (2.5)	65 (2.1)	0.350	0.026
liver dysfunction	30 (0.6)	67 (1.5)	<0.001	0.096	23 (0.7)	15 (0.5)	0.254	0.033
neuromuscular disease[a]	50 (0.9)	37 (0.8)	0.667	0.009	39 (1.3)	30 (1.0)	0.333	0.028
Type of surgery, n (%)								
neurological, head and neck	949 (17.8)	1027 (23.6)	<0.001	0.144	799 (26.0)	826 (26.8)	0.452	0.020
bone, joint, trauma, spine	725 (13.6)	837 (19.2)	<0.001	0.153	673 (21.9)	605 (19.7)	0.035	0.055
urological and kidney	209 (3.9)	635 (14.6)	<0.001	0.375	196 (6.4)	207 (6.7)	0.606	0.014
lower GI	478 (8.9)	595 (13.7)	<0.001	0.149	429 (13.9)	438 (14.2)	0.769	0.008
upper GI, hepatobiliary, pancreas	762 (14.3)	578 (13.3)	0.164	0.029	492 (16.0)	493 (16.0)	1.000	0.001
plastic, cutaneous and breast	777 (14.5)	243 (5.6)	<0.001	0.301	240 (7.8)	230 (7.5)	0.666	0.012
other	241 (4.5)	331 (7.6)	<0.001	0.130	219 (7.1)	238 (7.7)	0.382	0.024
vascular	102 (1.9)	206 (4.7)	<0.001	0.158	92 (3.0)	103 (3.3)	0.467	0.021
aortic	8 (0.1)	56 (1.3)	<0.001	0.135	7 (0.2)	9 (0.3)	0.803	0.013
endocrine	149 (2.8)	41 (0.9)	<0.001	0.137	38 (1.2)	39 (1.3)	1.000	0.003
transplant	12 (0.2)	21 (0.5)	0.035	0.043	12 (0.4)	11 (0.4)	1.000	0.005
Gynaecological[b]	1113 (20.8)	–	–	–	–	–	–	–
Urgency of surgery, n (%)			<0.001	0.080			0.978	0.006
elective	4821 (90.3)	3821 (87.8)			2713 (88.2)	2707 (88.0)		
urgent	404 (7.6)	412 (9.5)			286 (9.3)	291 (9.5)		
emergency	116 (2.2)	121 (2.8)			78 (2.5)	79 (2.6)		
Planned duration of surgery, minutes (median [IQR])	70 [41–120]	75 [42–132]	<0.001	0.114	70 [40–116]	70 [40–125]	0.014	0.078

Data presented as median with interquartile range (25th to 75th quartile) or % (n/total).
Abbreviations: SMD, standardized mean difference; BMI, body mass index; ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anaesthesiology physical status score; COPD, chronic obstructive pulmonary disease, GI = gastrointestinal.
[a] Any neuromuscular disease affecting the respiratory system.
[b] Gynaecological surgery patients were excluded before matching.

Table 2
Incidence of PPCs in unmatched and matched cohorts.

	unmatched cohort				matched cohort			
	female patients N = 5342	male patients N = 4355	p	OR [95% CI]	female patients N = 3077	male patients *N* = 3077	p	OR [95% CI]
Any PPC, n (%)	536 (10.0)	468 (10.7)	0.255	0.93 [0.81–1.06]	322 (10.5)	307 (10.0)	0.556	1.05 [0.89–1.25]
unplanned supplementary oxygen	459 (8.6)	367 (8.4)	0.798	1.02 [0.88–1.18]	271 (8.8)	241 (7.8)	0.181	1.14 [0.94–1.37]
respiratory failure	71 (1.3)	85 (2.0)	0.018	0.68 [0.49–0.94]	48 (1.6)	56 (1.8)	0.489	0.85 [0.57–1.28]
new invasive ventilation	45 (0.8)	62 (1.4)	0.008	0.59 [0.39–0.88]	32 (1.0)	39 (1.3)	0.474	0.82 [0.50–1.34]
pneumonia	15 (0.3)	25 (0.6)	0.026	0.49 [0.24–0.96]	10 (0.3)	15 (0.5)	0.423	0.67 [0.27–1.59]
pneumothorax	5 (0.1)	8 (0.2)	0.271	0.51 [0.13–1.77]	4 (0.1)	5 (0.2)	1.000	0.80 [0.16–3.72]
ARDS	3 (0.1)	6 (0.1)	0.315	0.41 [0.07–1.91]	2 (0.1)	4 (0.1)	0.687	0.50 [0.05–3.49]

PPC = Postoperative pulmonary complication; ARDS = Acute respiratory distress syndrome; OR = odds ratio; CI = confidence interval.

Table 3
Length of hospital stay, hospital discharge and hospital mortality in unmatched and matched cohorts.

	unmatched cohort				matched cohort			
	female patients N = 5342	male patients N = 4355	p	OR [95% CI]	female patients N = 3077	male patients N = 3077	p	OR [95% CI]
Length of hospital stay, days (median [IQR])	1 [0–4]	2 [0–5]	0.012	–	1 [0–4]	1 [0–4]	0.224	
hazard ratio for discharge with death as competing risk[a] [95% CI]	1.40 [0.78–2.51]	–	0.260	–	1.15 [0.56–2.35]	–	0.710	
hazard ratio for discharge among survivors[b] [95% CI]	1.04 [0.99–1.09]	–	0.120	–	0.94 [0.89–1.00]	–	0.039	
Hospital mortality, n (%)	23 (0.5)	28 (0.7)	0.160	0.67 [0.37–1.21]	14 (0.5)	19 (0.7)	0.388	1.37 [0.65–2.96]
hazard ratio[b] [95% CI]	0.74 [0.41–1.34]	–	0.320	–	0.82 [0.40–1.68]	–	0.590	

OR = odds ratio; CI = confidence interval; IQR = interquartile range;
[a] A Fine–Gray competing risk analysis was used.
[b] A cox shared–frailty model with centre as shared frailty was used.

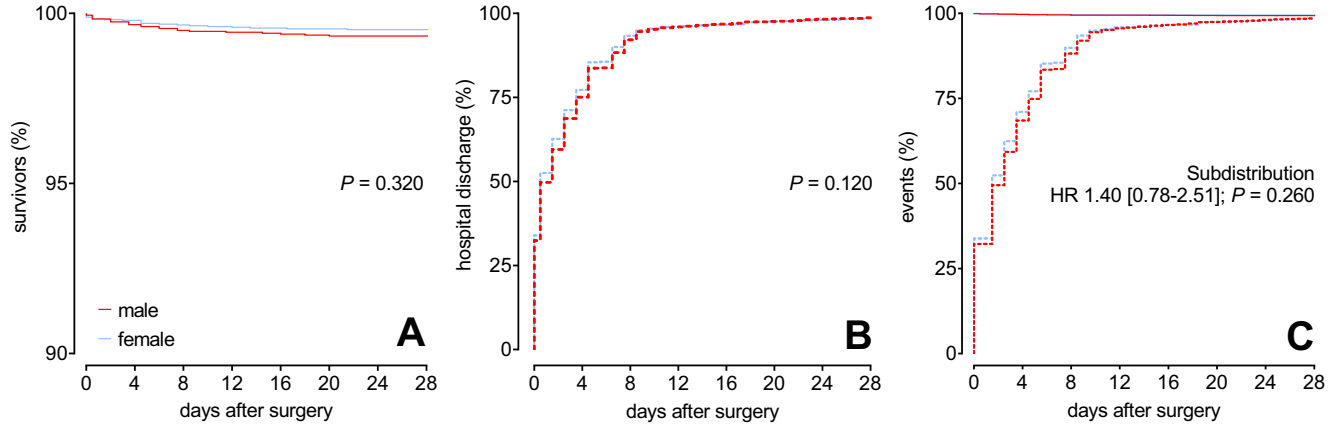


Fig. 2. Unmatched cohort. (A) cumulative incidence of survival, $N = 7985$, Cox shared frailty model; (B) cumulative incidence of hospital discharge among surviving patients, $N = 7940$, Cox shared frailty model; and (C) cumulative incidence of hospital discharge and survival, N = 7985, Fine–Gray competing risk analysis. Females are presented in blue, males in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

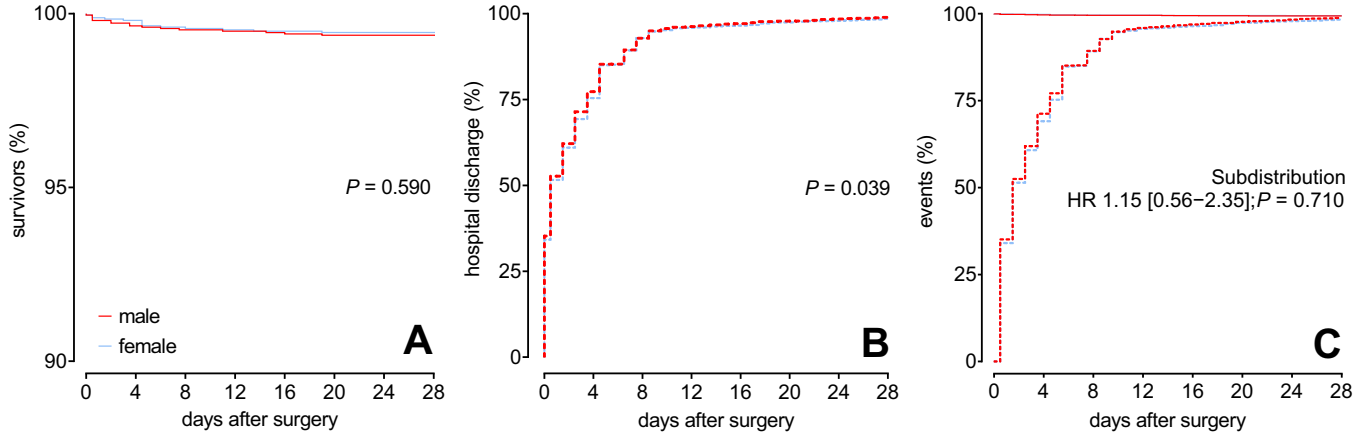


Fig. 3. Matched cohort. (A) cumulative incidence of survival, $N = 5165$, Cox shared frailty model; (B) cumulative incidence of hospital discharge among surviving patients, $N = 5135$, Cox shared frailty model; and (C) cumulative incidence of hospital discharge and survival, N = 5165, Fine–Gray competing risk analysis. Females are presented in blue, males in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

intraoperative ventilator settings, including V_T, are considered to be modifiable factors associated with PPCs [29], the current findings may seem surprising. Here, several aspects need to be considered. First, while critically ill females with ARDS receive more ventilation with a too high V_T, outcome seems only be worse when ARDS is severe [22]. Second, ventilation with a lower V_T may only be beneficial in ARDS patients with a low respiratory compliance, i.e., in patients with a low end–expiratory lung volume, while in ARDS patients with a higher or normal compliance it may worsen outcome, in particular when it is accompanied by a rise in the respiratory rate [30]. These findings may hold value for in the operating room, e.g., in patients that undergo intraoperative ventilation during general anaesthesia for minimally invasive or robotic–assisted

abdominal surgery. Pneumoperitoneum and the at times extreme Trendelenburg positioning will reduce end–expiratory lung volume [31], increasing the importance of using a lower V_T in that setting, in females and males. This suggestion is supported by another study demonstrating that the injurious effect of high V_T in the operating room is mediated by respiratory system elastance [32].

Our analysis has limitations. First, we could only assess PPCs that were collected as part of the original study [18]. In that study, only PPCs that could be captured as part of standard care were collected, limiting the generalizability of our results to PPCs we did not include. There is also no universally used and acceptable composite for PPCs, but the most recent consensus paper suggested to include a factor of severity in PPC reporting [33], which we did by reporting individual PPC incidences. Second, our findings might not be relevant to all patient groups. We excluded children, pregnant women, and patients undergoing specific surgeries from our analysis, so our results may not apply to them. Third, LAS VEGAS originated in 2013 [18]. Since then, there have been changes in how surgeries and anaesthesia are performed, such as the use of minimally invasive techniques and possibly alterations in intraoperative ventilation practices. These changes might have reduced the occurrence of complications and could thus affect the applicability of our findings. Fourth, despite our careful statistical analysis, there is always a chance that factors we did not consider might have influenced our findings. Due to the nature of observational studies, causality cannot be determined. It is important to note that propensity score matching carries the risk of concealing genuine distinctions between groups. Hence, these results should be interpreted as hypothesis generating and should not be considered as replacement of the findings from randomized controlled trials. Fifth, a sample size calculation was not performed, but we performed a post−hoc power calculation that showed our sample size was sufficient to detect what we defined as a clinically relevant difference. At last, our findings cannot estimate the direct effect of sex on PPCs [8,34,35]. The measured patient characteristics occur after the determination of sex. Therefore, the effect of sex obtained after adjustment for these characteristics is no longer the total effect of sex on the outcome, nor can the effect be interpreted as a direct effect [8]. Our results are exploratory and describe the association between sex and PPCs in a general surgical cohort, after which these findings are evaluated in a matched cohort in which the type of surgery and baseline PPC risk is similar.

5. Conclusions

Sex does not appear to correlate with PPCs, length of stay in hospital, and mortality in a general surgical population. Future investigations on sex–related disparities in PPCs should focus on subgroups at increased risk for PPCs, and maybe also on cohorts wherein it is difficult to apply protective intraoperative ventilation.

Authors statement

We would like to refer to the revised manuscript section 6 at page 18 line 380–391 for the details of all author's contributions.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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