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Multi-centre Evaluation of Renal Impairment in Thoracic Surgery (MERITS)

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Local coordinators and collaborators were involved in data collection.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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No Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval:
The project was approved by the Clinical Audit and Effectiveness Department at the study centre which was Royal Papworth Hospital, Cambridge (Registration Number: 1702) with a waiver for the need for patient consent and was approved as a multi-centre audit. This study was then registered as a clinical audit at each of

the collaborating hospitals. This study was supported by the Royal Papworth Hospital Research & Development Department and by SCTS STUDENTS, the student wing of the Society for Cardiothoracic Surgery in Great Britain & Ireland and the UK & Ireland Thoracic Surgery Forum

Transparency Statement:
The lead authors (VN and ASC) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Patient and Public Involvement statement:
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. No plans have been made to disseminate the results of the research to study participants.

Word count: 2996

KEYWORDS:

Acute Kidney Injury (AKI), Renal Impairment, Quality Improvement, Audit, Multicentre, Mortality, Length of stay, Thoracic Surgery.

What is already known about the topic?

- Acute Kidney Injury (AKI) is poorly documented and little studied in thoracic surgery, but has been extensively explored in other surgical fields in particular cardiac surgery
- Unit-based mortality in thoracic surgery is very low which limits its use as a comparative performance measure and thus drive quality improvement.
- There is a need to identify and validate additional outcome measures which can be easily measured and are associated with meaningful health and system outcomes. This study aims to assess AKI as such a performance measure.

What this study adds?

- MERITS is one of the largest studies ever conducted in acute kidney injury and thoracic surgery worldwide.
- Following thoracic surgery, there was significant variation of AKI incidence between units (3.1% - 16.1%).
- AKI is associated with prolonged hospital stay and higher 30-day, 90-day and 1-year mortality after thoracic surgery.
- We propose that AKI should be considered as a a suitable comparative and absolute quality measure in thoracic surgery. Reducing rates of AKI may bring about important improvements in patient outcomes and reduce costs. This will have wider healthcare system benefits.

ABSTRACT

Objectives- To measure the unit-level variation in AKI incidence post-thoracic surgery over a contemporary 1-year period. Secondary aims include examining the associations with sex, age, operation type, length of stay and mortality.

Design- A multi-centre, observational, retrospective study in thoracic surgery.

Setting- 17 of 35 UK thoracic surgery units participated. SCTS STUDENTS supported data collection.

Participants- Overall, 15229 patients were collected of which 15154 were included for analysis after exclusions. All patients (age≥18 years) undergoing any thoracic surgery from 01.04.2016 to 31.3.2017 were included. For analysis, we excluded patients with pre-operative end-stage renal failure and those with incomplete data.

Main Outcome measures- The primary outcome is the incidence of AKI within 7 days of the procedure or discharge date if earlier. Secondary outcomes include assessing associations with patient demographics (age, sex), type of procedure (open and minimally invasive), length of stay and mortality.

Results- 17 of 35 UK centres provided data on 15154 patients. AKI was diagnosed in 1090 patients (7.2%) within 7 days of surgery with AKI stage 1 (4.8%), stage 2 (1.7%) and stage 3 (0.7%). There was a statistically significant variation in AKI incidence between units from 3.1 to 16.1% ($p<0.05$). Significant differences between non-AKI and AKI were found in post-operative length of stay (3 vs 7 days, $p<0.001$), 30-day mortality (1.6 vs 9%, $p<0.001$), 90-day mortality (4.4 v 14.7%, $p<0.001$) and 1-year mortality (12.2 vs 23.1%, $p<0.001$).

Conclusions- Following thoracic surgery, AKI incidence ranged from 3.1% to 16.1% between units ($p<0.05$) with associations between AKI and both length of stay and mortality. We propose AKI as a suitable comparative and absolute quality measure in thoracic surgery. Reducing rates of AKI may improve patient outcomes, length of stay and reduce costs.

Strengths and limitations of this study

- MERITS is one of the largest studies ever conducted in acute kidney injury and thoracic surgery worldwide
- it is one of the largest collaborations of thoracic surgical units in the UK and was achieved without any extra funding. This was only possible because of a strong collaborative culture including students recruited from SCTS STUDENTS.
- The success of the project also relied on collecting simple, robust and pragmatic data variables that were previously identified in the pilot study.
- The observational design of this multi-centre study precludes conclusions regarding causal links between AKI and the outcomes.
- The study did not collect co-morbidities that have been previously associated with AKI as this was not the intent of the study objectives and design. This could be addressed in a future study.

MANUSCRIPT

INTRODUCTION

To achieve the best patient outcomes after surgery and drive quality improvement, suitable outcome measures are needed. Traditionally, mortality has been used, but because of improved care, mortality is now very low in thoracic surgery. The 2019 lung cancer clinical outcomes project (LCCOP) report (for operations in 2017) gave survival rates of 98.1% at 30 days and 88.7% at 1-year post-surgery for primary lung cancer in NHS England.[1] There were no negative outliers and one positive outlier at 30 days. At one year, there were no outliers. In the SCTS thoracic surgery audit[2] from 1st April 2016- 31st March 2017, 28,740 cases in total were reported to the SCTS from units in the UK and Republic of Ireland. The overall in-hospital unadjusted mortality rate for this period was 1.16% (334 deaths/28,740 cases). This is reassuring for patients and clinicians. However, when an outcome has little variation, it means that there are limitations in using it to compare performance.

As a result, there is a need to identify and validate additional outcome measures. Such a metric should be easy to reliably measure, be associated with meaningful health and system outcomes and show sufficient variation. This study aims to assess acute kidney injury (AKI) as such a performance measure.
Acute Kidney Injury (AKI) is not well documented in thoracic surgery. Only three relevant publications report an incidence of AKI post-thoracic surgery: 5.9% after all lung resections,[3] and 6.8% and 10% after lung cancer resections.[4,5] AKI is well recognised after cardiac surgery and is associated with worse morbidity, mortality and more costs.[6–9] AKI has been studied in other surgical fields with rates from 6-12% in gastrointestinal surgery and 23-25% in vascular surgery.[10]

Our previous single-centre pilot study found an incidence of AKI post-thoracic surgery of 15.1% (86/568).[11] AKI was also associated with a longer hospital stay. However, in order to explore variation, a single centre study is not sufficient. Having wider, multi-centre estimates of incidence and baseline characteristics of AKI after thoracic surgery would allow benchmarking and quality improvement and standards to guide practice. In order to better understand AKI in thoracic surgery, we developed this project: “Multicentre Evaluation of Renal Impairment in Thoracic Surgery” (MERITS).
In this study, which we now report, we observed significant variation of AKI incidence across the participating centres and found that AKI was associated with increased length of stay and mortality.
The primary aim was to determine the unit-level variation in the incidence of AKI post thoracic surgery over a contemporary 1-year period. Secondary aims were to report the associations with sex, age, operation type, length of stay and mortality.

METHODS

Study design

MERITS is a multi-centre, observational, retrospective study in thoracic surgery, composed of a collaboration of 17 thoracic surgery centres participating in the SCTS thoracic surgery national rolling audit.

All 35 hospitals in the UK and Ireland that offer adult thoracic surgery and report to the SCTS thoracic surgery audit were invited. Seventeen units participated. Each participating thoracic surgery unit team comprised a consultant thoracic surgeon lead, a day-to-day coordinator (usually a middle-grade doctor or a research nurse), and a group of medical students recruited by SCTS STUDENTS.

Inclusion and Exclusion criteria:

All patients (age ≥ 18 years) undergoing any thoracic surgery from 1st April-2016 to 31st March-2017 (date of 1st surgery within these dates) were included. For analysis, we excluded patients with pre-operative end-stage renal failure and those with incomplete data.

Variables:

Our previous pilot study[11] had led us to select variables which appeared to be both pragmatic to collect, robust and clinically meaningful. These were: submitted SCTS thoracic surgery operation code; dates of birth, operation, discharge, death (if applicable); sex; AKI stage (1, 2 or 3); peak creatinine; pre and post-operative renal replacement therapy. Thoracic surgery operations were recorded using the nationally accepted SCTS code for 2016/17 (Supplementary file 1). Survival was collected for 1-year post-surgery.

To accurately collect renal function data, each thoracic unit contacted their respective biochemistry department and extracted the AKI stage and peak creatinine up to 7 days from the operation or discharge date if earlier. AKI stage was calculated using the algorithm introduced by the NHS England Patient Safety Alert to standardise AKI identification.[12] In 3 of 17 units, creatinine was collected manually, and the AKI staging was calculated following the same algorithm.

Our pilot study[11] found that urine volumes were not collected or recorded reliably; therefore, we did not collect this in MERITS. In modern thoracic surgery practice within our nations, urinary catheterisation and strict urine volume recording is not commonly performed, and so urine output is not a robust measure.

Outcome measures

The primary outcome is the incidence of AKI occurring within 7 days of the procedure or discharge date if earlier. Secondary outcomes include assessing associations with patient demographics (age, sex), type of procedure (open and minimally invasive), length of stay and mortality.

Data quality, security and validation:

The majority of data collectors were medical students who were recruited by SCTS STUDENTS and junior doctors. All participants were provided with an online training package as part of the local site set-up. They were supervised by a day-to-day coordinator (ranging from a middle-grade cardiothoracic surgeon to a research nurse) and a consultant surgeon. Data was entered locally onto a spreadsheet with each team securely retaining a non-anonymised version. A secure anonymised version was sent to the MERITS study centre. Validation with each centre was performed before analysis. Digital security followed GDPR guidelines.

Data were validated by two observers who were not involved in the original data collection. Individual unit analysis was shared with each unit lead for checking and approval.

Data collection period:

The launch for MERITS was in March 2018 at the SCTS Annual Meeting in Glasgow. This was followed by local regulatory approvals. Site opening and the recruitment of students and other data collectors took place during Summer 2018. All participants were provided with site packs with access to key documents for the study design, including on-line training videos.[13]

Statistical analysis:

Continuous variables were summarised with the following descriptive statistics, non-missing sample size, mean and 95% and 99.8% confidence intervals or medians with interquartile range (IQR) where appropriate. Categorical data such as AKI incidence was summarised using frequencies and percentages calculated using the non-missing sample size. Univariate hypothesis testing was undertaken by Mann Whitney U tests for continuous data and Chi-squared for categorical data.

Multivariate analysis was also undertaken using generalised linear mixed modelling (GLMM) to assess the associations between AKI incidence and the fixed effects of our covariates plus random variation in intercept among centres. Our fixed effects include age group (Young/Old/Oldest), sex (M/F) and operation type (Open/VATs/Endoscopic). All centres were included as random effect intercepts with a fixed gradient. Model fit was assessed by the Hosmer-Lemeshow goodness of fit test, by computing receiver operating characteristics and Nakagawa's pseudo r^2 for mixed effect models. The associations of the fixed effects were estimated and reported as odds ratios with 95% confidence intervals. The conditional modes of the random effect intercepts and their 95% confidence intervals were also derived to assess centre specific variation in isolation from fixed effects.

Ethics, approval and dissemination:

The project was approved by the Clinical Audit and Effectiveness Department at the study centre which was Royal Papworth Hospital, Cambridge (Registration Number: 1702). with a waiver for the need for patient consent and was approved as a multi-centre audit. This study was then registered as a clinical audit at each of the collaborating hospitals. The protocol and invitation to participate was disseminated widely through local and national student networks and societies in the UK and Ireland.

Patient and Public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. No plans have been made to disseminate the results of the research to study participants.

RESULTS

Subjects

Overall, 15229 patients were collected of which 15154 were included for analysis after exclusions (Figure 1). These were from 17 out of 35 thoracic surgical units in the UK. Unit operative volumes ranged from 304 to 2,416 patients per year. The total number of thoracic surgery operations submitted to SCTS in 2016-17 was 28740. This study represented 52.7% of all operations reported.

Table 1 shows the sex, age groups, whether open, VATS or endoscopic and SCTS operation code category are shown along with the proportion with and without AKI.

Demographics

8809 (58.1%) patients were male and 6345 (41.9%) were female.
Average age at operation was 60.72 ± 16.76 years. Age was divided into 3 categories; 5958 (39.3%) were <60 years, 8197 (54.1%) was 60-79 years and 998 (6.6%) were ≥ 80 years. One patient's age was not reliably confirmed.

Minimally invasive versus open surgery

The breakdown of operations as completed was as follows: 5835 (38.5%) operations were open, 7635 (50.4%) were minimally invasive video-assisted thoracic surgery (VATS), 1684 (11.1%) were endoscopic (such as bronchoscopy). 20 cases were reported as robotic and were included with the minimally invasive VATS group.

SCTS operation code category

The breakdown of operations is shown in Table 1. The largest categories were lung resections for primary lung cancer (category A, 4502 cases, 29.8%), pleural diseases (category D, 3311 cases, 21.8%) and lung resections for reasons other than lung cancer (category B, 1930 cases, 12.8%). All lung resections (categories A and B) accounted for 42.6% of the workload.

Characteristics of AKI

Incidence of AKI

Of 15154 patients, 1090 (7.2%) were found to have developed AKI within 7 days post-thoracic surgery: stage 1 (n= 731; 4.8%); stage 2 (n=255; 1.7%); and stage 3 (n=104; 0.7%). AKI incidence ranged between 3.1% to 16.1%. The units have been listed in rank order from 1 to 17 (with 1 being the lowest rate of AKI and 17 the highest). This is shown numerically in Table 2 and Forest plot Figure 2.

AKI rate in open and minimally invasive surgery

Patients who had open surgery had a higher rate of AKI as compared to those who had VATS (Table 1). Of those that did not develop AKI, 37.4% of patients had open surgery, 51.1% had VATS and 11.5% had an endoscopy. Of those that did develop AKI, 52.8% of patients had open surgery, 41.7% had VATS and 5.5% had an endoscopy.

Adjusted AKI variation across units

To assess centre variation and associations more accurately between our covariates and AKI incidence we undertook a multivariate analysis. Using the GLMM framework, we adjusted our observed clinically relevant variables by defining our fixed effects terms as age group, sex and operation type with each centre represented by a random effect intercept with a fixed gradient.

All fixed effects showed a significant relationship with developing AKI post operatively. Male patients had a 1.37x (CI 95% 1.21-1.57; P<0.001) increased odds of developing AKI. Patients between the age of 60-79 had a 1.99x (CI 95% 1.72-2.30; P<0.001) increased odds of developing AKI; and above 80 had a 3.01x (CI 95% 2.4-3.8; P<0.001) increased odds of developing AKI. There was a 1.7x (CI 95% 1.48-1.94; P<0.001) increased odds of developing AKI with open procedures compared to VATS (Table 3).

We then derived the conditional mode of the random intercepts for each centre to assess the adjusted centre to centre variation (Figure 3). We found that there was significant variation in 64.7% (11/17) of the sampled centres after adjusting for our observed covariates. This suggests that there was significant variation across the centres.

Model diagnostics showed no evidence of lack of fit (HL test, p = 0.32), and a reasonable level of discrimination with a c-statistic of 0.71. However, our model did not explain much of the variability in the data (Conditional pseudo $r^2 = 0.15$), meaning there are likely unobserved explanatory covariates.

Length of stay

Patients with AKI (as compared to those without) had an increased median postoperative length of stay of 4 days as compared to non-AKI (7 v 3 days; p<0.001) (Table 4).

The total increase in length of stay accounts for 4360 days across the 1090 AKI-positive patients or 5.1% (4360/86054) of the total number of days spent in the hospital after thoracic surgery in our study population.

Mortality

Patients with AKI (as compared to those without) had a significantly increased mortality at 30-days (AKI 9% vs no AKI 1.6%; p<0.001); 90 day (14.7% v 4.4%) and 1 year (23.1 vs 12.2%; p<0.001) (Table 4).

Across centres, we found that mortality varied between 0.3%-5.1% at 30 days, 2.0%-9.6% at 90 days and 3.2%-19.0% at 1 year (Figure 4 a-c). Interestingly, we observed that the ranking of AKI differed from the ranking of mortality. For instance, the unit with the highest rate of AKI, did not have the highest level of mortality.

DISCUSSION

MERITS is the largest study to examine AKI after thoracic surgery and one of the largest such studies in a surgical population.[3–5] Previous single centre studies showed AKI rates that varied from 5.9% after all lung resections[3] to 6.8% and 10% after lung cancer resections.[4,5] Our earlier single-centre pilot study incorporating all procedures found a rate of 15.1%.[11]

The primary aim was to examine the variation in AKI incidence between units. This study of 17 units in the UK found an overall AKI rate of 7.2% with a range from 3.1% to 16.1%. The spread was statistically significant. We have also shown that the post-thoracic surgery AKI variation was greater than the postoperative death rate reported in a similar period. In the 2019 LCCOP report, the overall in-hospital mortality was 1.26% (334 of 26460 patients) with 1 positive outlier at 30 days and no outliers at 1 year. We have shown that AKI has a greater variation in incidence than the death rate. In this study after adjustment, there are 5 positive and 6 negative statistical outliers (Figure 3), which would support the use of AKI as a performance metric.

This study showed the variation in AKI between units is greater than the variation in mortality. However, there was not a consistent relationship between AKI and mortality. For example, the unit with the highest rate of AKI (unit 17 in Table 1 and Figure 2 and 3) had a much lower mortality rate. The explanation for this is not obvious, and it is likely multifactorial. One explanation is that in that unit post-operative steps effectively treat AKI though do not prevent its occurrence as compared to other units. Examining the case-mix and different practices

between units will be the start of exploring the reasons for this difference and this can drive quality improvement.

We went on to demonstrate a statistically significant association between AKI and length of stay and mortality. There are many studies in different clinical situations which observe similar findings. It is recognised that AKI is an independent predictor of death[14] even with mild transient AKI post-surgery.[15] Patients who develop AKI are at increased risk of chronic kidney disease and end-stage renal failure.[16]

Because AKI is sometimes preventable and reducing its rate is associated with better outcomes, there are important potential health and economic benefits of monitoring and reducing AKI rates.[17] There is a national programme in the UK to increase AKI awareness and to prevent and treat it.

The relationship between AKI and longer stay is also intuitively clear. In this study, the associated unadjusted median increase in bed occupancy is 5.1%, corresponding to 4360 days. While there will be various contributory factors, it follows that reducing postoperative AKI is also likely to reduce the length of stay.

We found that increased age and male sex were also associated with an increased risk of AKI. Various reasons can be speculated. Renal function declines with age and the nephrotoxic impact of surgery and anaesthesia may be greater. Perioperative hypotension for example may be less well tolerated.

Importantly, we found that open surgery is associated with a significantly greater risk of AKI than minimally invasive surgery. The reasons for this may be related to the greater tissue injury associated with an open operation, but there could also be other factors such as complexity and length of the surgery. We speculate that the latter is more likely and this is another area to be explored.

This study has several strengths. MERITS is one of the largest studies ever conducted in acute kidney injury and thoracic surgery worldwide. Furthermore, it is one of the largest collaborations of thoracic surgical units in the UK and was achieved without any extra funding. This was only possible because of a strong collaborative culture including students recruited from SCTS STUDENTS. The success of the project also relied on collecting simple, robust and pragmatic data variables that were previously identified in the pilot study.
This study has some limitations. The observational design of this multi-centre study precludes conclusions regarding causal links between AKI and the outcomes. AKI was diagnosed based on renal function only as urine output data could not be collected reliably. The study did not collect co-morbidities that have been previously associated with AKI as this was not the intent of the study objectives and design. This could be addressed in a future study.

In summary, we have identified a significant variation in AKI rates post thoracic surgery. This variation between units will be due to multiple factors and reflect different surgical and anaesthetic strategies as well as patient heterogeneity. This is likely to include different approaches to perioperative cardiac output control, fluid management and use of nephrotoxic agents. Historically patients undergoing thoracic surgery were often relatively dehydrated on the basis that this may reduce the rate of acute lung injury associated with positive-pressure ventilation and surgical trauma. This is different to some of the concepts of enhanced recovery which encourage hydration and euvolaemia. It would be useful to consider the approach of the better performing units to determine what practices could be disseminated in line with the quality improvement strategy of the NHS.[18]

TABLES

Table 1. Age, sex, operation mode and SCTS code and proportion with AKI

	level	Overall	AKI Negative	AKI Positive
n		15154	14064	1090
Gender n (%)	F	6345 (41.9)	5967 (42.4)	378 (34.7)
	M	8809 (58.1)	8097 (57.6)	712 (65.3)
Age group n (%)	Young	5958 (39.3)	5686 (40.4)	272 (25.0)
	Old	8197 (54.1)	7500 (53.3)	697 (63.9)
	Oldest	998 (6.6)	877 (6.2)	121 (11.1)
Operation access mode n (%)	OPEN	5835 (38.5)	5260 (37.4)	575 (52.8)
	VATS	7635 (50.4)	7180 (51.1)	455 (41.7)
	ENDO	1684 (11.1)	1624 (11.5)	60 (5.5)
SCTS operation code category n (%)	A	4502 (29.8)	4052 (28.9)	450 (41.5)
	B	1930 (12.8)	1812 (12.9)	118 (10.9)
	C	452 (3.0)	416 (3.0)	36 (3.3)
	D	3311 (21.9)	3084 (22.0)	227 (20.9)
	E	734 (4.9)	693 (4.9)	41 (3.8)
	F	1484 (9.8)	1433 (10.2)	51 (4.7)
	G	50 (0.3)	41 (0.3)	9 (0.8)
	H	13 (0.1)	12 (0.1)	1 (0.1)
	I	939 (6.2)	847 (6.0)	92 (8.5)
	Z	1684 (11.2)	1624 (11.6)	60 (5.5)

Table 2. AKI incidence (%) by unit in rank order

Anonymised Centre ID	Centre Size	AKI Negative	AKI Positive
1	1233	1195 (96.9)	38 (3.1)
2	1267	1227 (96.8)	40 (3.2)
3	1037	1003 (96.7)	34 (3.3)
4	497	480 (96.6)	17 (3.4)
5	716	691 (96.5)	25 (3.5)
6	615	587 (95.4)	28 (4.6)
7	1341	1265 (94.3)	76 (5.7)
8	513	482 (94.0)	31 (6.0)
9	716	668 (93.3)	48 (6.7)
10	1413	1308 (92.6)	105 (7.4)
11	458	423 (92.4)	35 (7.6)
12	518	473 (91.3)	45 (8.7)
13	645	586 (90.9)	59 (9.1)
14	2384	2122 (89.0)	262 (11.0)
15	922	807 (87.5)	115 (12.5)
16	301	262 (87.0)	39 (13.0)
17	578	485 (83.9)	93 (16.1)

Table 3. AKI modelling for gender, age and operation type.

			95% confidence intervals		
		Odds ratio	Lower bound	Upper bound	P value
	(Intercept)	0.03	0.02	0.04	<0.001
Gender	Female	1.00	Reference		
	Male	1.37	1.20	1.57	<0.001
Age	Youngest	1.00	Reference		
	Old	1.99	1.72	2.30	<0.001
	Oldest	3.02	2.40	3.80	<0.001
Operation Type	VATS	1.00	Reference		
	OPEN	1.70	1.48	1.94	<0.001
	Endoscopy	0.54	0.41	0.71	<0.001

Table 4. Associations between AKI and mortality and length of stay

	Level	AKI Negative	AKI Positive	p
N		14064	1090	
30 day Mortality (%)	Survived	13846 (98.4)	992 (91.0)	<0.001
	Died	218 (1.6)	98 (9.0)	
90 Day mortality (%)	Survived	13451 (95.6)	930 (85.3)	<0.001
	Died	613 (4.4)	160 (14.7)	
365 Day Mortality (%)	Survived	12354 (87.8)	838 (76.9)	<0.001
	Died	1710 (12.2)	252 (23.1)	
Length of stay (median [IQR])		3.00 [2.00, 6.00]	7.00 [4.00, 13.00]	<0.001

FIGURES

Figure 1. Flow chart of inclusion and exclusion of patients.

Figure 2. Unadjusted Forest Plot for AKI incidence amongst different units.
Point ranges report the AKI proportion of that centre and the associated 95% confidence interval. The solid horizontal line is the mean AKI incidence across all centres and the dashed lines represent the associated 95% and 99.8% confidence intervals.

Figure 3. Adjusted Forest Plot for AKI incidence amongst different units.
Point ranges represent the estimated conditional mode of the random intercept associated with each centre with the associated 95% confidence intervals. Brown points represent centres that deviate significantly from average and black points represent non-significant centres.

Figure 4a-c: Unadjusted Forest plot for 30-day, 90 day and 1 year mortality among different units. Point ranges report the proportion of mortality of that centre and the associated 95% confidence interval. The solid horizontal line is the mean mortality across all centres and the dashed lines represent the associated 95% and 99.8% confidence intervals.

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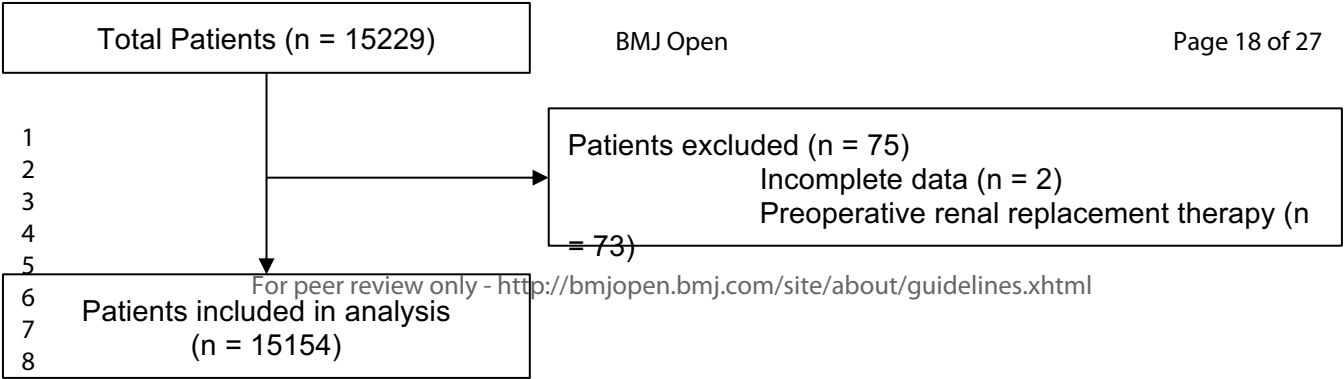

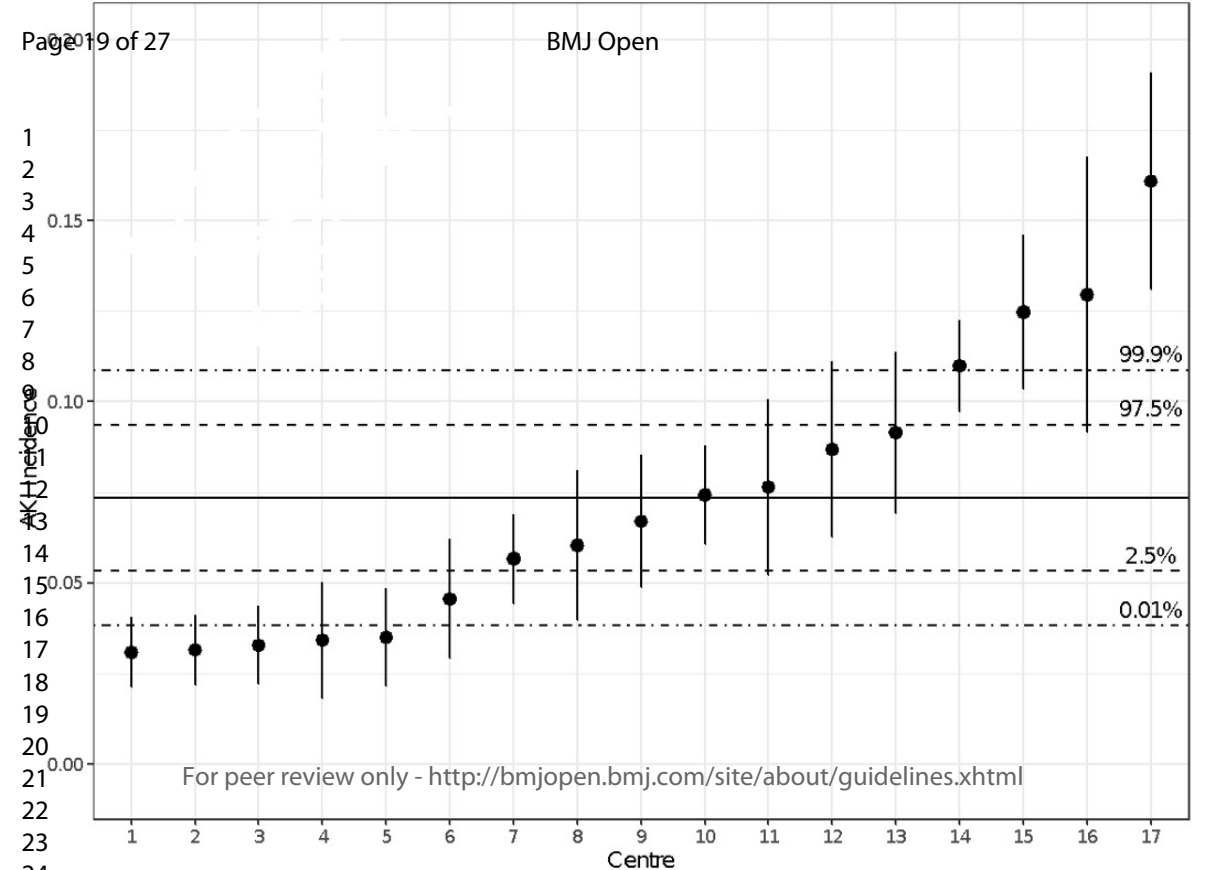

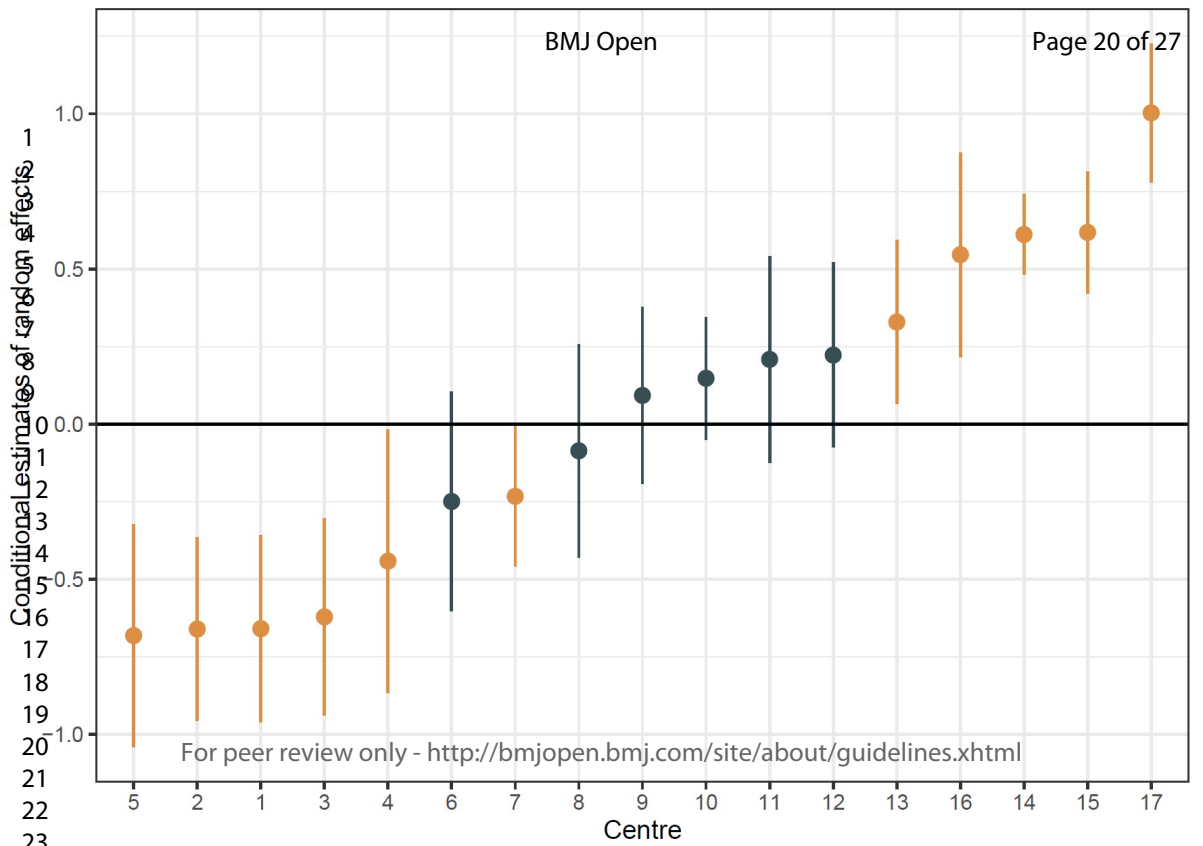

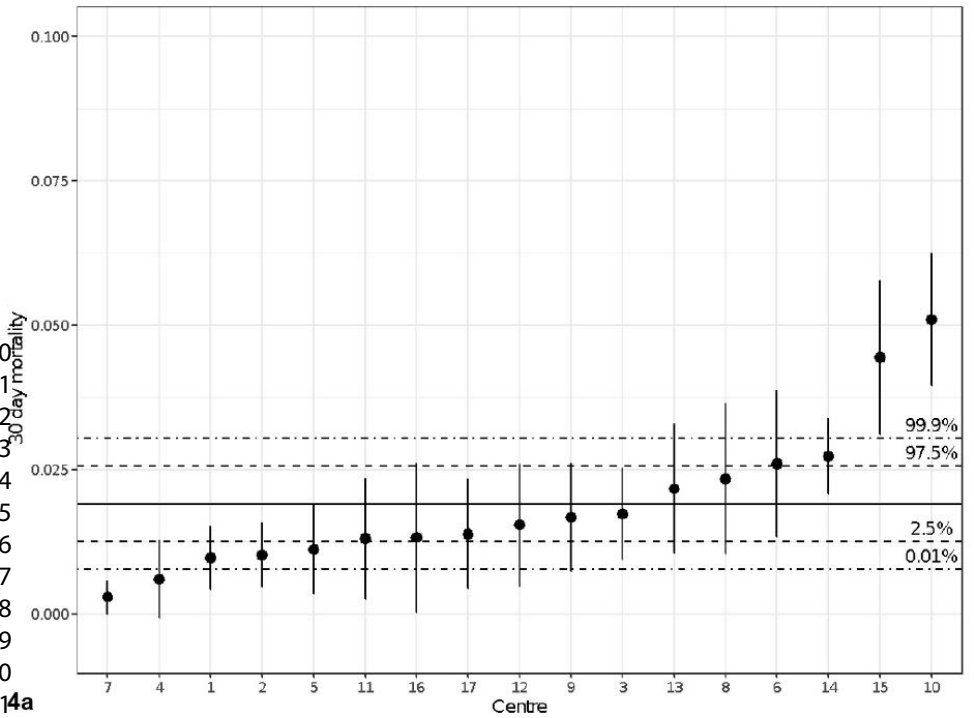

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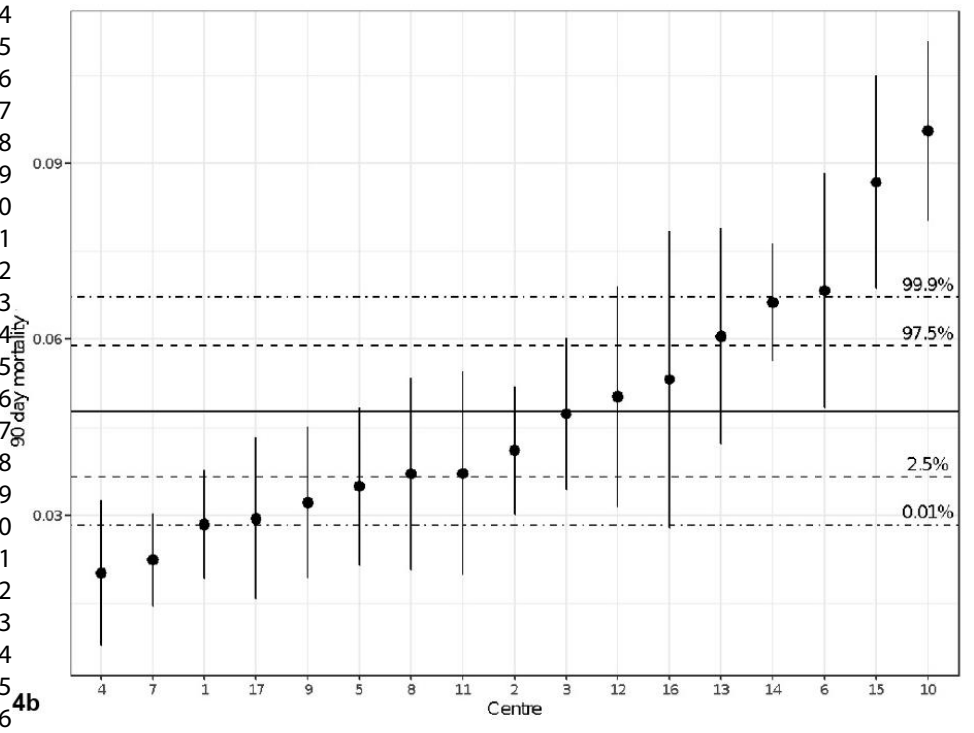

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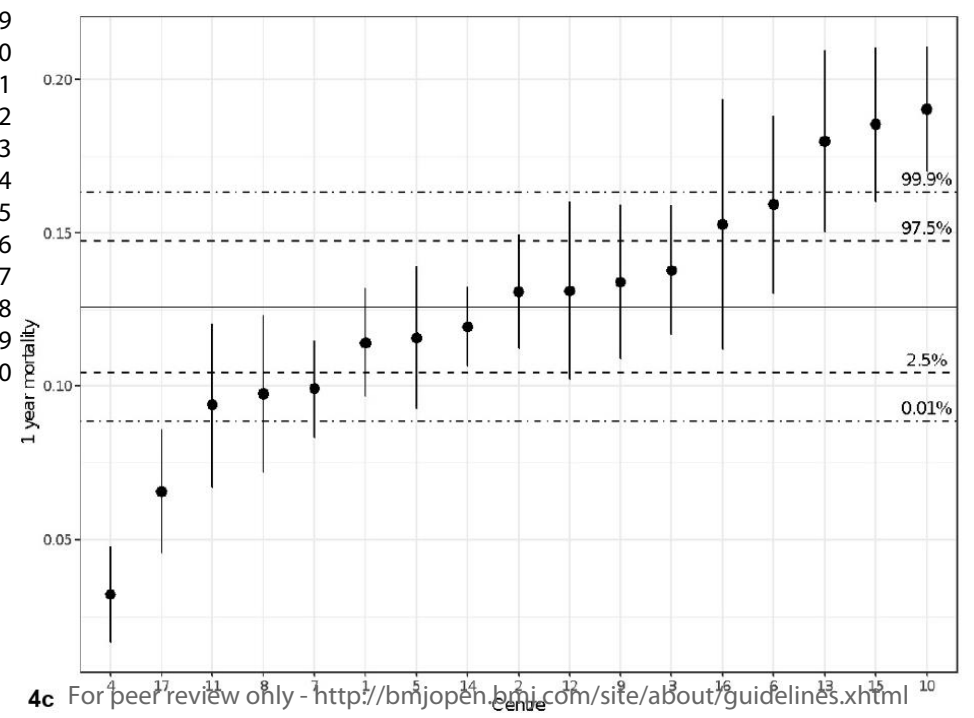

4c

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Supplementary file 1.

A LUNG RESECTIONS - PRIMARY-MALIGNANT

1 Pneumonectomy including sleeve pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection lobectomy

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc

7 Exploratory procedure - no resection

B LUNG RESECTIONS - ALL OTHER PATHOLOGIES

1 Pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc

7 Open lung volume reducion surgery for emphysema

8 Other pulmonary procedure

C MESOTHELIOMA SURGERY (THERAPEUTIC)

1 Extrapleural pneumonectomy

2 Extended pleurectomy / decortication

3 Pleurectomy/decortication

4 Partial pleurectomy

D PLEURAL PROCEDURES - OTHER

1 Decortication for empyema

2 Pneumothorax surgery (pleural symphysis +/- closure of air leak) Other pleural procedures

E CHEST WALL/DIAPHRAGMATIC PROCEDURES

1. Correction of pectus deformity (code Nuss/MIRPE in "thoracoscopic" column) 2 Resection of primary chest wall tumour (not lung cancer)

3 Other major

4 Minor

F MEDIASTINAL PROCEDURES

1 Thymectomy for thymoma

2 Thymectomy for myasthenia gravis

3 Throidectomy

4 Resection of other mediastinal mass/tumour 5 Mediastinoscopy / mediastinotomy

6 Other mediastinal proceudure

G OESOPHAGEAL/GASTRIC PROCEDURES

1 Oesophago-gastric resection - malignant

2 Oesophago-gastric resection - non-malignant

3 Other major oesophagogastric

4 Exploration only by any route for inoperable tumour 5 Minor oesophagogastric

H TRACHEAL SURGERY (includes carinal resection)

1 Tracheal resection - tumour

2 Tracheal resection - non-tumour

I OTHER PROCEDURES

1 Major

2 Minor

VATS- A LUNG RESECTIONS - PRIMARY-MALIGNANT

1 Pneumonectomy including sleeve pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection lobectomy

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc 7 Exploratory procedure - no resection

VATS- B LUNG RESECTIONS - ALL OTHER PATHOLOGIES

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2 Lobectomy, bilobectomy

3 Sleeve resection lobectomy

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc 7 Open lung volume reducion surgery for emphysema

8 Other pulmonary procedure

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2 Extended pleurectomy / decortication

3 Pleurectomy/decortication

4 Partial pleurectomy

VATS- D PLEURAL PROCEDURES - OTHER

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2 Pneumothorax surgery (pleural symphysis +/- closure of air leak)

3 Other pleural procedures

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3 Other major

4 Minor

VATS- F MEDIASTINAL PROCEDURES

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2 Thymectomy for myasthenia gravis

3 Throidectomy

4 Resection of other mediastinal mass/tumour 5 Mediastinoscopy / mediastinotomy

6 Other mediastinal proceudure

VATS- G OESOPHAGEAL/GASTRIC PROCEDURES

1 Oesophago-gastric resection - malignant

2 Oesophago-gastric resection - non-malignant

3 Other major oesophagogastric

4 Exploration only by any route for inoperable tumour

5 Minor oesophagogastric

VATS- H TRACHEAL SURGERY (includes carinal resection)

1 Tracheal resection - tumour

2 Tracheal resection - non-tumour

VATS- I OTHER PROCEDURES

1 Major

2 Minor

Z Endoscopic Procedures (Not VATS)

1 Therapeutic bronchoscopy

2 Therapeutic oesophagoscopy

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	6

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,6
		(b) Give reasons for non-participation at each stage	5,6
		(c) Consider use of a flow diagram	5,6,14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,6,7
		(b) Indicate number of participants with missing data for each variable of interest	5,6,7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7,8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7,8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Multi-centre Evaluation of Renal Impairment in Thoracic Surgery (MERITS): a retrospective cohort study

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Renal medicine
Keywords:	Thoracic surgery < SURGERY, AUDIT, Acute renal failure < NEPHROLOGY

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Multi-centre Evaluation of Renal Impairment in Thoracic Surgery (MERITS): a retrospective cohort study

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Steering committee: involved in validation and reviewing the manuscript.
Thoracic Centre Principal Investigators from each centre held responsibility over data collection and validation.
Local coordinators and collaborators were involved in data collection.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interest:
No Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval:
The project was approved by the Clinical Audit and Effectiveness Department at the study centre which was Royal Papworth Hospital, Cambridge (Registration Number: 1702) with a waiver for the need for patient consent and was approved as a multi-centre audit. This study was then registered as a clinical audit at each of the collaborating hospitals. This study was supported by the Royal Papworth Hospital Research & Development Department and by SCTS STUDENTS, the student wing of the Society for Cardiothoracic Surgery in Great Britain & Ireland and the UK & Ireland Thoracic Surgery Forum. Data received from the participating units was anonymised before the authors accessed it for the purpose of this study.

Transparency Statement:
The lead authors (VN and ASC) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Role of the funding source:
Statistical support was provided from the MRC Biostatistics Unit Cambridge through the Papworth Trials Unit Collaboration. No additional funds were used, and the work was done on a voluntary basis by all the collaborators.

Data Sharing

All data was anonymised before being accessed for purpose of this study. Data was retrospectively collected for the year 2016/17. Data analysed is included within the article and raw data are available upon reasonable request.

Word count: 3050

KEYWORDS:

Acute Kidney Injury (AKI), Renal Impairment, Quality Improvement, Audit, Multicentre, Mortality, Length of stay, Thoracic Surgery.

ABSTRACT

Objectives- To measure the unit-level variation in AKI incidence post-thoracic surgery over a contemporary 1-year period. Secondary aims include examining the associations with sex, age group, operation type, length of stay and mortality.

Design- A multi-centre, observational, retrospective study in thoracic surgery.

Setting- 17 of 35 UK thoracic surgery units participated. SCTS STUDENTS supported data collection.

Participants- Overall, 15229 patients were collected of which 15154 were included for analysis after exclusions. All patients (age≥18 years) undergoing any thoracic surgery from 01.04.2016 to 31.3.2017 were included. For analysis, we excluded patients with pre-operative end-stage renal failure and those with incomplete data.

Main Outcome measures- The primary outcome is the incidence of AKI within 7 days of the procedure or discharge date if earlier. Secondary outcomes include assessing associations with patient demographics (age, sex), type of procedure (open and minimally invasive), length of stay and mortality.

Results- 17 of 35 UK centres provided data on 15154 patients. AKI was diagnosed in 1090 patients (7.2%) within 7 days of surgery with AKI stage 1 (4.8%), stage 2 (1.7%) and stage 3 (0.7%). There was a statistically significant variation in AKI incidence between units from 3.1 to 16.1% ($p<0.05$). Significant differences between non-AKI and AKI were found in post-operative length of stay (3 vs 7 days, $p<0.001$), 30-day mortality (1.6 vs 9%, $p<0.001$), 90-day mortality (4.4 v 14.7%, $p<0.001$) and 1-year mortality (12.2 vs 23.1%, $p<0.001$).

Conclusions- Following thoracic surgery, AKI incidence ranged from 3.1% to 16.1% between units ($p<0.05$) with associations between AKI and both length of stay and mortality. We propose AKI as a suitable comparative and absolute quality measure in thoracic surgery. Reducing rates of AKI may improve patient outcomes, length of stay and reduce costs.

Strengths and limitations of this study

- MERITS is one of the largest studies in acute kidney injury and thoracic surgery worldwide
- We collected simple, robust and pragmatic data variables that were previously identified in the pilot study.
- The observational design of this multi-centre study does not allow conclusions regarding causal links between AKI and the outcomes.
- The study did not collect co-morbidities that have been previously associated with AKI as this was not the intent of the study objectives and design.

MANUSCRIPT

INTRODUCTION

To achieve the best patient outcomes after surgery and drive quality improvement, suitable outcome measures are needed. Traditionally, mortality has been used, but because of improved care, mortality is now very low in thoracic surgery. The 2019 lung cancer clinical outcomes project (LCCOP) report (for operations in 2017) gave survival rates of 98.1% at 30 days and 88.7% at 1-year post-surgery for primary lung cancer in NHS England.[1] There were no negative outliers and one positive outlier at 30 days. At one year, there were no outliers. In the Society for Cardiothoracic Surgery of Great Britain and Ireland (SCTS) thoracic surgery audit [2] from 1st April 2016- 31st March 2017, 28,740 cases in total were reported to the SCTS from units in the UK and Republic of Ireland. The overall in-hospital unadjusted mortality rate for this period was 1.16% (334 deaths/28,740 cases). This is reassuring for patients and clinicians. However, when an outcome has little variation, it means that there are limitations in using it to compare performance.

As a result, there is a need to identify and then validate additional outcome measures. Such a metric should be i. easy to reliably measure, ii. be associated with meaningful health and system outcomes and iii. show sufficient variation. This study aims to assess acute kidney injury (AKI) [3] as such a performance measure.

Acute Kidney Injury (AKI) is not well documented in thoracic surgery. Only three relevant publications report an incidence of AKI post-thoracic surgery: 5.9% after all lung resections,[4] and 6.8% and 10% after lung cancer resections.[5,6] AKI is well recognised after cardiac surgery and is associated with worse morbidity, mortality and more costs.[7–10] AKI has been studied in other surgical fields with rates from 6-12% in gastrointestinal surgery and 23-25% in vascular surgery.[11]

Our previous single-centre pilot study found an incidence of AKI post-thoracic surgery of 15.1% (86/568).[12] AKI was also associated with a longer hospital stay. However, in order to explore variation, a single centre study is not sufficient. Having multi-centre estimates of incidence and baseline characteristics of AKI after thoracic surgery would allow benchmarking and quality improvement and standards to guide practice. In order to better understand AKI in thoracic surgery, we developed this project: "Multicentre Evaluation of Renal Impairment in Thoracic Surgery" (MERITS).

The primary aim was to determine the unit-level variation in the incidence of AKI post thoracic surgery over a contemporary 1-year period. Secondary aims were to report associations with sex, age, operation type, length of stay and mortality. This study is not designed to show causation.

We now report significant variation of AKI incidence post thoracic surgery across the participating centres and found that AKI was associated with increased length of stay and mortality.

METHODS

Study design

MERITS is a multi-centre, observational, retrospective study in thoracic surgery, composed of a collaboration of 17 thoracic surgery centres participating in the already established SCTS thoracic surgery rolling audit. SCTS includes the thoracic surgery units from 5 different national health care systems (Eire, England, Scotland, Northern Ireland and Wales)

All 35 hospitals in the UK and Ireland that offer adult thoracic surgery and report to the SCTS thoracic surgery audit were invited. Seventeen units participated. Each participating thoracic surgery unit team comprised a consultant thoracic surgeon lead, a day-to-day coordinator (usually a middle-grade doctor or a research nurse), and a group of medical students recruited by SCTS STUDENTS.

Inclusion and Exclusion criteria:

All patients (age ≥ 18 years) undergoing any thoracic surgery from 1st April-2016 to 31st March-2017 (date of 1st surgery within these dates) were included. For analysis, we excluded patients with pre-operative end-stage renal failure and those with incomplete data.

Variables:

Our previous pilot study [12] had identified variables which were both pragmatic to collect, robust and clinically meaningful. These were: the submitted SCTS thoracic surgery operation code (please refer to Supplementary file 1 and Table 1), dates of birth, operation, discharge, death (if applicable); sex; AKI stage (1, 2 or 3); peak creatinine; pre and post-operative renal replacement therapy. Thoracic surgery operations were recorded using the accepted SCTS code for 2016/17. Survival was collected for 1-year post-surgery.

To accurately collect renal function data, each thoracic unit contacted their respective biochemistry department and extracted the AKI stage and peak creatinine up to 7 days from the operation or discharge date if earlier. AKI stage was calculated using the algorithm introduced by the NHS England Patient Safety Alert to standardise AKI identification.[13] In 3 of 17 units, creatinine was collected manually, and the AKI staging was calculated following the same algorithm.

Our pilot study [12] had previously found that urine volumes were not collected or recorded reliably; therefore, we did not collect this in MERITS. In modern thoracic surgery practice within our nations, urinary catheterisation and strict urine volume recording is not commonly performed, and so urine output is not a robust measure.

Outcome measures

The primary outcome is the incidence of AKI occurring within 7 days of the procedure or discharge date if earlier. Secondary outcomes include assessing associations with patient demographics (age group, sex), type of procedure (open and minimally invasive), length of stay and mortality.

Data quality, security and validation:

The majority of data collectors were medical students who were recruited by SCTS STUDENTS and junior doctors. All participants were provided with an online training package as part of the local site set-up. They were supervised by a day-to-day coordinator (usually a middle-grade cardiothoracic surgeon or a research nurse) and a consultant surgeon. Data was entered locally onto a spreadsheet with each team securely retaining a non-anonymised version. A secure anonymised version was sent to the MERITS study centre. Validation with each centre was performed before analysis. Digital security followed GDPR guidelines.

Data were validated by two observers who were not involved in the original data collection. Individual unit analysis was shared with each unit lead for checking and approval.

Data collection period:

The launch for MERITS was in March 2018 at the SCTS Annual Meeting in Glasgow. This was followed by local regulatory approvals. Site opening and the recruitment of students and other data collectors took place during Summer 2018. All participants were provided with site packs with access to key documents for the study design, including on-line training videos.[14]

Statistical analysis:

Continuous variables were summarised with the following descriptive statistics, non-missing sample size, mean and 95% and 99.8% confidence intervals or medians with interquartile range (IQR) where appropriate. Categorical data such as AKI incidence was summarised using frequencies and percentages calculated using the non-missing sample size. Univariate hypothesis testing was undertaken by Mann Whitney U tests for continuous data and Chi-squared for categorical data.

Multivariate analysis was also undertaken using generalised linear mixed modelling (GLMM) to assess the associations between AKI incidence and the fixed effects of our covariates plus random variation in intercept among centres. Our fixed effects include age group (Young <60 years / Old 60-79 years / Oldest Old ≥ 80 years) [15,16], sex (M/F) and operation type (Open/VATs/Endoscopic). All centres were included as random effect intercepts with a fixed gradient. Model fit was assessed by the Hosmer-Lemeshow goodness of fit test, by computing receiver operating characteristics and Nakagawa's pseudo r^2 for mixed effect models. The associations of the fixed effects were estimated and reported as odds ratios with 95% confidence intervals. The

conditional modes of the random effect intercepts and their 95% confidence intervals were also derived to assess centre specific variation in isolation from fixed effects.

Ethics, approval and dissemination:

The project was approved by the Clinical Audit and Effectiveness Department at the study centre which was Royal Papworth Hospital, Cambridge (Registration Number: 1702) with a waiver for the need for patient consent and was approved as a multi-centre audit. This study was then registered as a clinical audit at each of the collaborating hospitals. The protocol and invitation to participate was disseminated widely through student networks and societies in the UK and Ireland.

Patient and Public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. No plans have been made to disseminate the results of the research to study participants.

Patient and Public Involvement statement:

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RESULTS

Subjects

Overall, 15229 patients were collected of which 15154 were included for analysis after exclusions (Figure 1). These were from 17 out of 35 thoracic surgical units in the UK. Unit operative volumes ranged from 304 to 2416 patients per year. The total number of thoracic surgery operations submitted to SCTS in 2016-17 was 28740. This study represented 52.7% of all operations reported.

Table 1 shows the sex, age groups, whether open, VATS or endoscopic and SCTS operation code category are shown along with the proportion with and without AKI.

Demographics

8809 (58.1%) patients were male and 6345 (41.9%) were female.

Average age at operation was 60.7 ± 16.8 years. Age was divided into 3 categories; 5958 (39.3%) were <60 years, 8197 (54.1%) was 60-79 years and 998 (6.6%) were ≥ 80 years. One patient's age was not reliably confirmed.

Minimally invasive versus open surgery

The breakdown of operations as completed was as follows: 5835 (38.5%) operations were open, 7635 (50.4%) were minimally invasive video-assisted thoracic surgery (VATS), 1684 (11.1%) were endoscopic (such as bronchoscopy). 20 cases were reported as robotic and were included with the minimally invasive VATS group.

SCTS operation code category

The breakdown of operations is also shown in Table 1. The largest categories were lung resections for primary lung cancer (category A, 4502 cases, 29.8%), pleural diseases (category D, 3311 cases, 21.8%) and lung resections for reasons other than lung cancer (category B, 1930 cases, 12.8%). All lung resections (categories A and B) accounted for 42.6% of the workload.

Characteristics of AKI

Incidence of AKI

Of 15154 patients, 1090 (7.2%) were found to have developed AKI within 7 days post-thoracic surgery: stage 1 (n= 731; 4.8%); stage 2 (n=255; 1.7%); and stage 3 (n=104; 0.7%). AKI incidence ranged between 3.1% to 16.1%. The units have been listed in rank order from 1 to 17 (with 1 being the lowest rate of AKI and 17 the highest). This is shown numerically in Table 2 and Forest plot Figure 2.

AKI rate in open and minimally invasive surgery

9.9% of patients undergoing open surgery developed AKI versus 6.0% undergoing VATS and 3.6% undergoing endoscopic procedures (Table 1).

Adjusted AKI variation across units

To assess centre variation and associations more accurately between our covariates and AKI incidence we undertook a multivariate analysis. Using the GLMM framework, we adjusted our observed clinically relevant variables by defining our fixed effects terms as age group, sex and operation type with each centre represented by a random effect intercept with a fixed gradient.

All fixed effects showed a significant relationship with developing AKI post operatively. Male patients had a 1.37x (CI 95% 1.21-1.57; P<0.001) increased odds of developing AKI. Patients between the age of 60-79 had a 1.99x (CI 95% 1.72-2.30; P<0.001) increased odds of developing AKI; and above 80 had a 3.01x (CI 95% 2.4-3.8; P<0.001) increased odds of developing AKI. There was a 1.7x (CI 95% 1.48-1.94; P<0.001) increased odds of developing AKI with open procedures compared to VATS (Table 3).

We then derived the conditional mode of the random intercepts for each centre to assess the adjusted centre to centre variation (Figure 3). We found that there was significant variation in 11/17 (64.7%) of the sampled centres after adjusting for our observed covariates. This suggests that there was significant variation across the centres.

Model diagnostics showed no evidence of lack of fit (HL test, p = 0.32), and a reasonable level of discrimination with a c-statistic of 0.71. However, our model did not explain much of the variability in the data (Conditional pseudo $r^2 = 0.15$), meaning there are likely to be unobserved explanatory covariates.

Length of stay

Patients with AKI (as compared to those without) had an increased median postoperative length of stay of 4 days as compared to non-AKI (7 v 3 days; p<0.001) (Table 4).

The total increase in length of stay accounts for 4360 days across the 1090 AKI-positive patients or 5.1% (4360/86054) of the total number of days spent in the hospital after thoracic surgery in our study population.

Mortality

Patients with AKI (as compared to those without) had a significantly increased mortality at 30-days (AKI 9% vs no AKI 1.6%; p<0.001); 90 day (14.7% v 4.4%) and 1 year (23.1 vs 12.2%; p<0.001) (Table 4).

Across centres, we found that mortality varied between 0.3%-5.1% at 30 days, 2.0%-9.6% at 90 days and 3.2%-19.0% at 1 year (Figure 4 a-c). We observed that the ranking of AKI differed from the ranking of mortality. For instance, the unit with the highest rate of AKI, did not have the highest level of mortality. We also observed that the ranking of mortality changed over the three time points.

DISCUSSION

MERITS is the largest study to examine AKI after thoracic surgery and one of the largest such studies in a surgical population.[4–6] Previous single centre studies showed AKI rates that varied from 5.9% after all lung resections [4] to 6.8% and 10% after lung cancer resections.[5,6] Our earlier single-centre pilot study incorporating all procedures found a rate of 15.1%.[12]

The primary aim was to examine the unit variation in AKI incidence after thoracic surgery. This study of 17 units found an overall AKI rate of 7.2% with a range from 3.1% to 16.1%. The spread was statistically significant.

We have also shown that the post-thoracic surgery AKI variation was greater than the postoperative death rate reported in a similar period. In the 2019 LCCOP report, the overall in-hospital mortality was 1.26% (334 of 26460 patients) with 1 positive unit outlier at 30 days and no unit outliers at 1 year.

Thus, we have shown that AKI has a greater variation in incidence than the death rate. In this study after adjustment, there are 5 positive and 6 negative statistical unit outliers (Figure 3), which would support the use of AKI as a performance metric.

This study showed the variation in AKI between units is greater than the variation in mortality. However, there was not a consistent relationship between AKI and mortality. For example, the unit with the highest rate of AKI (unit 17 in Table 1 and Figure 2 and 3) had a much lower mortality rate. The explanation for this is not obvious, and it is likely to be multifactorial. One explanation is that in that unit post-operative steps effectively treat AKI though do not prevent its occurrence as compared to other units. Examining the case-mix and different practices between units will be the start of exploring the reasons for this difference and this can drive quality improvement.

We went on to demonstrate a statistically significant association between AKI and length of stay and mortality. There are many studies in different clinical situations which observe similar findings. It is recognised that AKI is an independent predictor of death [17] even with mild transient AKI post-surgery.[18] Patients who develop AKI are at increased risk of chronic kidney disease and end-stage renal failure.[19]

Because AKI is sometimes preventable and reducing its rate is associated with better outcomes, there are important potential health and economic benefits of monitoring and reducing AKI rates.[20] There is a national programme in the UK to increase AKI awareness and to prevent and treat it.

The relationship between AKI and longer stay is also intuitively clear. In this study, the associated unadjusted median increase in bed occupancy is 5.1%, corresponding to 4360 days. While there will be various contributory factors, it follows that reducing postoperative AKI is also likely to reduce the length of stay.

We found that increased age and male sex were also associated with an increased risk of AKI. Various reasons can be speculated. Renal function declines with age and the nephrotoxic impact of surgery and anaesthesia may be greater. Perioperative hypotension for example may be less well tolerated.

Importantly, we found that open surgery is associated with a significantly greater risk of AKI than minimally invasive surgery. The reasons for this may be related to the greater tissue injury associated with an open operation, but there could also be other factors such as complexity and length of the surgery. We speculate that the latter is more likely and this is another area to be explored.

MERITS is one of the largest studies ever conducted in acute kidney injury and thoracic surgery worldwide. Furthermore, it is one of the largest collaborations of thoracic surgical units in the UK and was achieved without any extra funding. This was only possible because of a strong collaborative professional culture including students recruited from SCTS STUDENTS. The success of the project also relied on collecting simple, robust and pragmatic data variables that were previously identified in the pilot study.

This study has some limitations. The observational design of this multi-centre study precludes conclusions regarding causal links between AKI and the outcomes. AKI was diagnosed based on renal function only as urine output data could not be collected reliably. We were reliant on the coding of cases according to the SCTS database. The categorisation is high-level and no intraoperative details are collected. The study also did not collect co-morbidities that have been previously associated with AKI as this was not the intent of the study objectives and design. This could be addressed in a future study.

In summary, we have identified a significant variation in AKI rates between units post thoracic surgery. This will be due to multiple factors and reflect different surgical and anaesthetic strategies as well as patient heterogeneity. This is likely to include different approaches to perioperative cardiac output control, fluid management and use of nephrotoxic agents. Historically patients undergoing thoracic surgery were often relatively dehydrated on the basis that this may reduce the rate of acute lung injury associated with positive-

pressure ventilation and surgical trauma. This is different to some of the concepts of enhanced recovery which encourage hydration and euvolaemia.[21] It would be useful to consider the approach of the better performing units to determine what practices could be disseminated in line with the quality improvement strategy of the NHS.[22]

TABLES

Table 1. Age, sex, operation mode and SCTS code and proportion with AKI

n	level	Overall 15154	AKI Negative 14064	AKI Positive 1090
Gender n (%)	F	6345	5967 (94.0)	378 (6.0)
	M	8809	8097 (91.9)	712 (8.1)
Age group n (%)	Young	5958	5686 (95.4)	272 (4.6)
	Old	8197	7500 (91.5)	697 (8.5)
	Oldest	998	877 (87.9)	121 (12.1)
Operation access mode n (%)	OPEN	5835	5260 (90.1)	575 (9.9)
	VATS	7635	7180 (94.0)	455 (6.0)
	ENDO	1684	1624 (96.4)	60 (3.6)
SCTS operation code category n (%)	A – lung resections (primary malignant)	4502	4052 (90.0)	450 (10.0)
	B – lung resections (all other pathologies)	1930	1812 (93.9)	118 (6.1)
	C – mesothelioma surgery (therapeutic)	452	416 (92.0)	36 (8.0)
	D – pleural procedures (other)	3311	3084 (93.1)	227 (6.9)
	E – chest wall/diaphragmatic procedures	734	693 (94.4)	41 (5.6)
	F – mediastinal procedures	1484	1433 (96.6)	51 (3.4)
	G – oesophageal/gastric procedures	50	41 (82.0)	9 (18)
	H – tracheal surgery	13	12 (92.3)	1 (7.7)
	I – other procedures	939	847 (90.2)	92 (9.8)
	Z – endoscopic procedures	1684	1624 (96.4)	60 (3.6)

Table 2. AKI incidence (%) by unit in rank order

Anonymised Centre ID	Centre Size	AKI Negative	AKI Positive
1	1233	1195 (96.9)	38 (3.1)
2	1267	1227 (96.8)	40 (3.2)
3	1037	1003 (96.7)	34 (3.3)
4	497	480 (96.6)	17 (3.4)
5	716	691 (96.5)	25 (3.5)
6	615	587 (95.4)	28 (4.6)
7	1341	1265 (94.3)	76 (5.7)
8	513	482 (94.0)	31 (6.0)
9	716	668 (93.3)	48 (6.7)
10	1413	1308 (92.6)	105 (7.4)
11	458	423 (92.4)	35 (7.6)
12	518	473 (91.3)	45 (8.7)
13	645	586 (90.9)	59 (9.1)
14	2384	2122 (89.0)	262 (11.0)
15	922	807 (87.5)	115 (12.5)
16	301	262 (87.0)	39 (13.0)
17	578	485 (83.9)	93 (16.1)

Table 3. AKI modelling for gender, age and operation type.

			95% confidence intervals		
		Odds ratio	Lower bound	Upper bound	P value
	(Intercept)	0.03	0.02	0.04	<0.001
Gender	Female	1.00	Reference		
	Male	1.37	1.20	1.57	<0.001
Age	Youngest (<60)	1.00	Reference		
	Old (60-79)	1.99	1.72	2.30	<0.001
	Oldest (80+)	3.02	2.40	3.80	<0.001
Operation Type	VATS	1.00	Reference		
	OPEN	1.70	1.48	1.94	<0.001
	Endoscopy	0.54	0.41	0.71	<0.001

Table 4. Associations between AKI and mortality and length of stay

	Level	AKI Negative	AKI Positive	p
N		14064	1090	
30 day Mortality (%)	Survived	13846 (98.4)	992 (91.0)	<0.001
	Died	218 (1.6)	98 (9.0)	
90 Day mortality (%)	Survived	13451 (95.6)	930 (85.3)	<0.001
	Died	613 (4.4)	160 (14.7)	
365 Day Mortality (%)	Survived	12354 (87.8)	838 (76.9)	<0.001
	Died	1710 (12.2)	252 (23.1)	
Length of stay (median [IQR])		3.00 [2.00, 6.00]	7.00 [4.00, 13.00]	<0.001

FIGURES

Figure 1. Flow chart of inclusion and exclusion of patients.

Figure 2. Unadjusted Forest Plot for AKI incidence amongst different units.
Point ranges report the AKI proportion of that centre and the associated 95% confidence interval. The solid horizontal line is the mean AKI incidence across all centres and the dashed lines represent the associated 95% and 99.8% confidence intervals.

Figure 3. Adjusted Forest Plot for AKI incidence amongst different units.
Point ranges represent the estimated conditional mode of the random intercept associated with each centre with the associated 95% confidence intervals. Brown points represent centres that deviate significantly from average and black points represent non-significant centres.

Figure 4a-c: Unadjusted Forest plot for 30-day, 90 day and 1 year mortality among different units. Point ranges report the proportion of mortality of that centre and the associated 95% confidence interval. The solid horizontal line is the mean mortality across all centres and the dashed lines represent the associated 95% and 99.8% confidence intervals.

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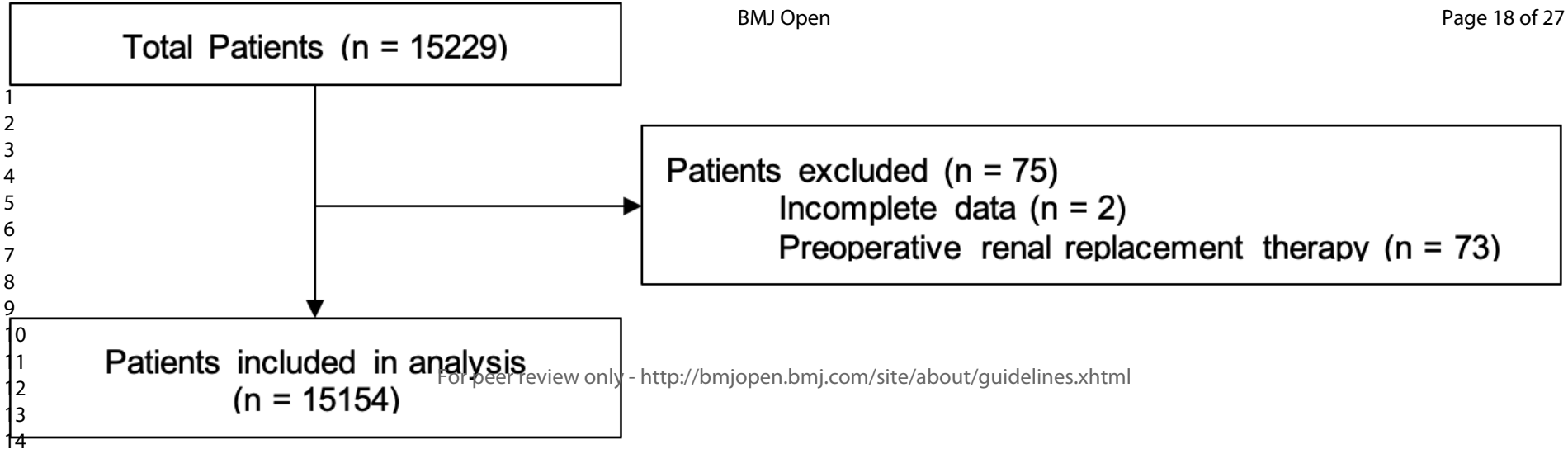

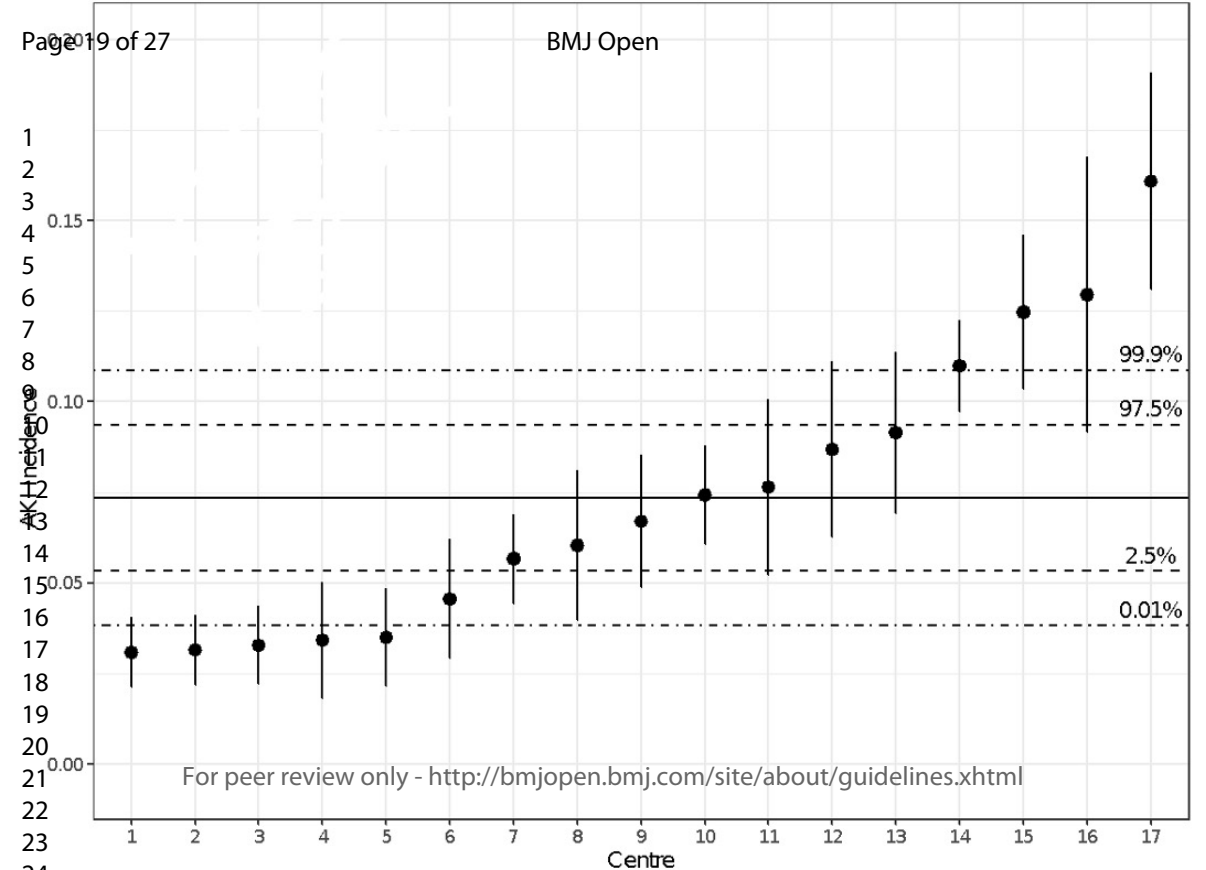

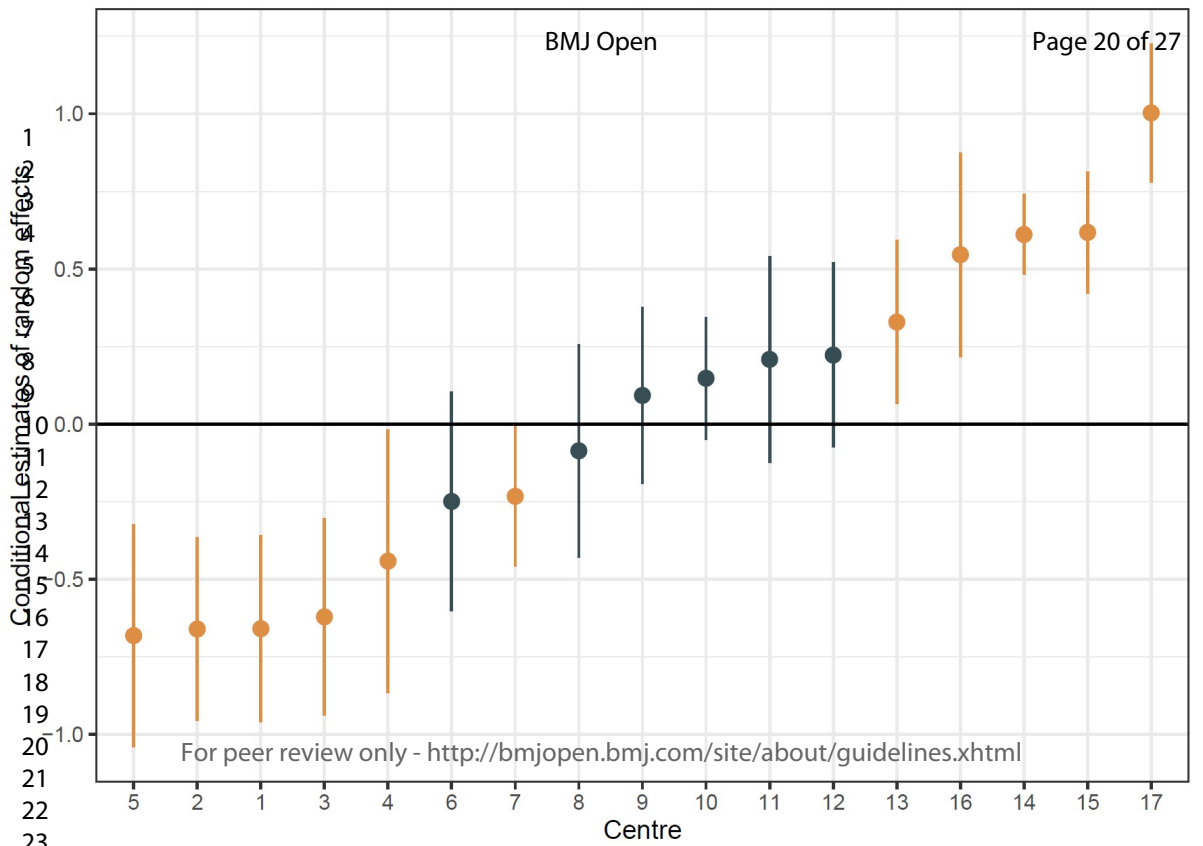

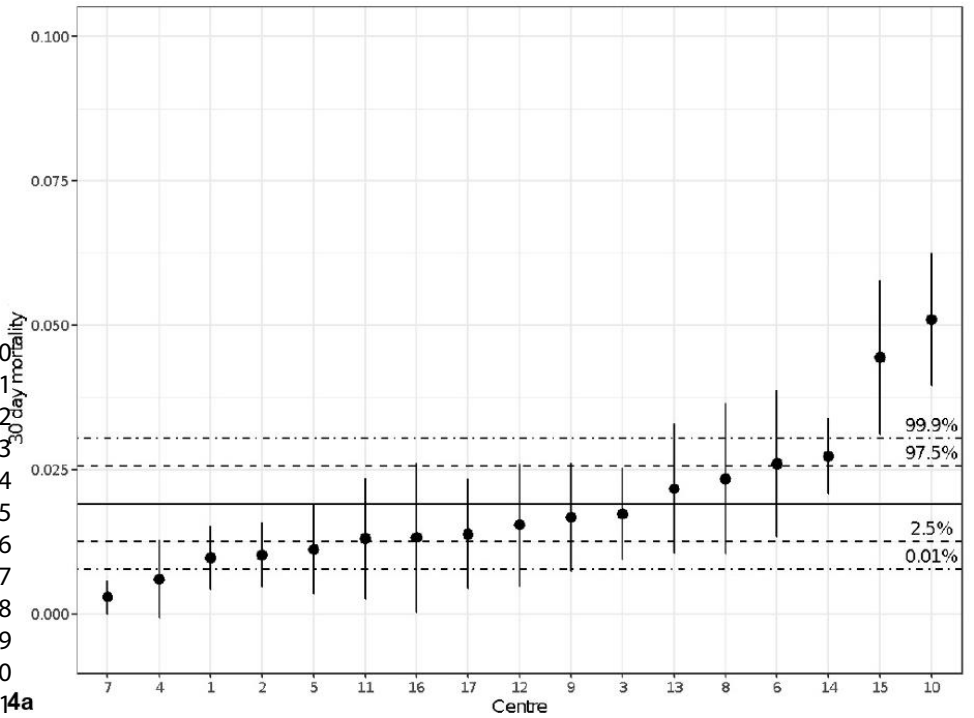

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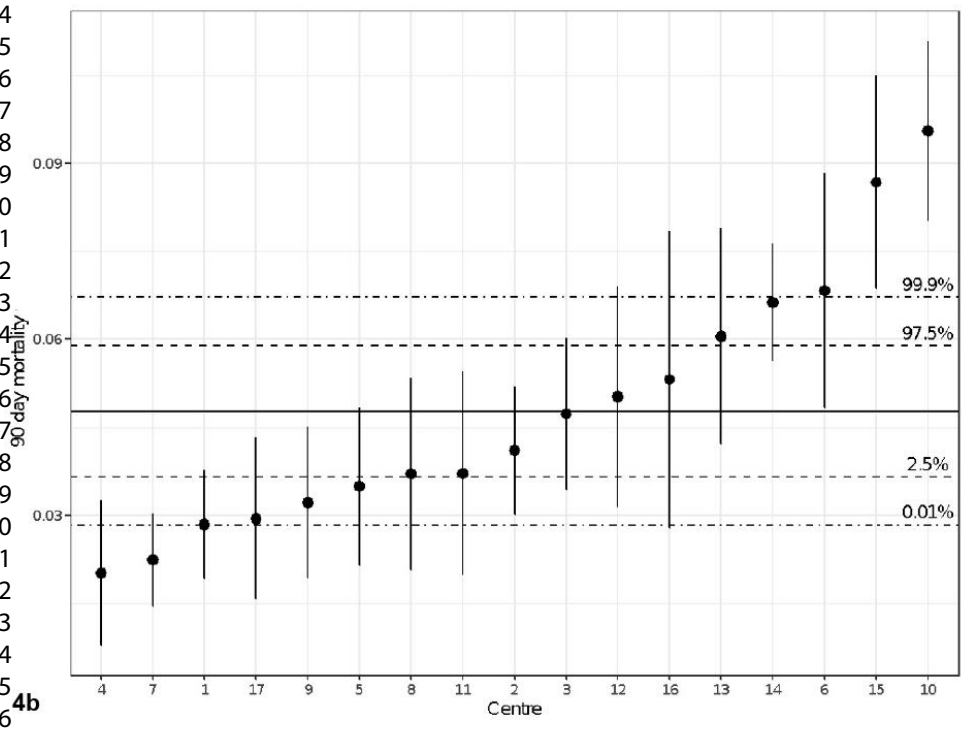

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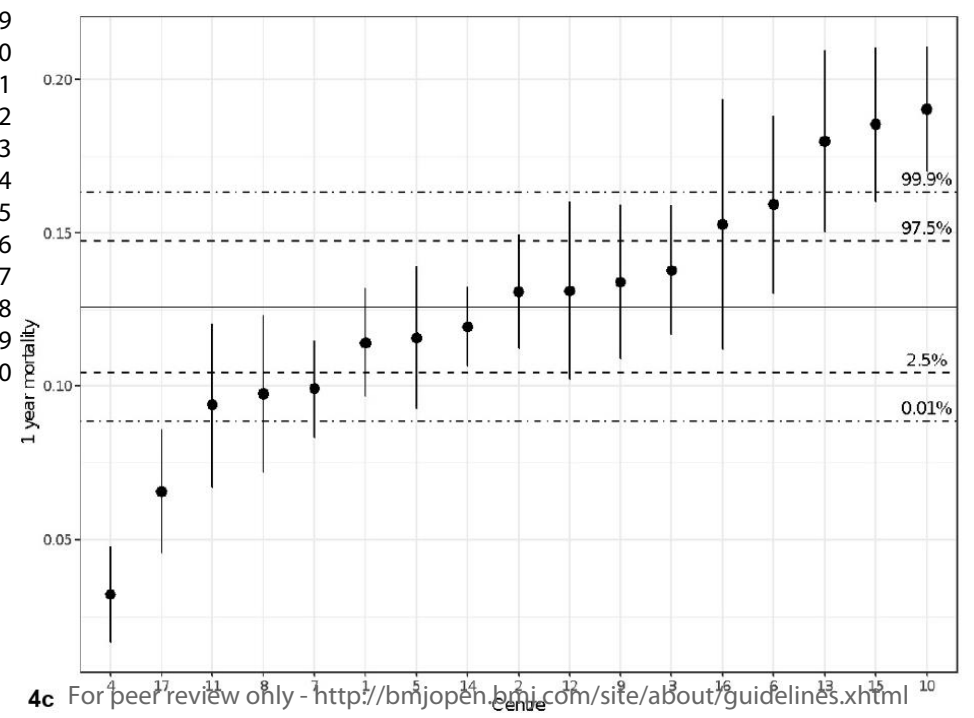

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Supplementary file 1.

A LUNG RESECTIONS - PRIMARY-MALIGNANT

1 Pneumonectomy including sleeve pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection lobectomy

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc

7 Exploratory procedure - no resection

B LUNG RESECTIONS - ALL OTHER PATHOLOGIES

1 Pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc

7 Open lung volume reducion surgery for emphysema

8 Other pulmonary procedure

C MESOTHELIOMA SURGERY (THERAPEUTIC)

1 Extrapleural pneumonectomy

2 Extended pleurectomy / decortication

3 Pleurectomy/decortication

4 Partial pleurectomy

D PLEURAL PROCEDURES - OTHER

1 Decortication for empyema

2 Pneumothorax surgery (pleural symphysis +/- closure of air leak) Other pleural procedures

E CHEST WALL/DIAPHRAGMATIC PROCEDURES

1. Correction of pectus deformity (code Nuss/MIRPE in "thoracoscopic" column) 2 Resection of primary chest wall tumour (not lung cancer)

3 Other major

4 Minor

F MEDIASTINAL PROCEDURES

1 Thymectomy for thymoma

2 Thymectomy for myasthenia gravis

3 Throidectomy

4 Resection of other mediastinal mass/tumour 5 Mediastinoscopy / mediastinotomy

6 Other mediastinal proceudure

G OESOPHAGEAL/GASTRIC PROCEDURES

1 Oesophago-gastric resection - malignant

2 Oesophago-gastric resection - non-malignant

3 Other major oesophagogastric

4 Exploration only by any route for inoperable tumour 5 Minor oesophagogastric

H TRACHEAL SURGERY (includes carinal resection)

1 Tracheal resection - tumour

2 Tracheal resection - non-tumour

I OTHER PROCEDURES

1 Major

2 Minor

VATS- A LUNG RESECTIONS - PRIMARY-MALIGNANT

1 Pneumonectomy including sleeve pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection lobectomy

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc 7 Exploratory procedure - no resection

VATS- B LUNG RESECTIONS - ALL OTHER PATHOLOGIES

1 Pneumonectomy

2 Lobectomy, bilobectomy

3 Sleeve resection lobectomy

4 Segmentectomy

5 Wedge resection

6 Any pulmonary resection with resection of chest wall, diaphragm etc 7 Open lung volume reducion surgery for emphysema

8 Other pulmonary procedure

VATS- C MESOTHELIOMA SURGERY (THERAPEUTIC)

1 Extrapleural pneumonectomy

2 Extended pleurectomy / decortication

3 Pleurectomy/decortication

4 Partial pleurectomy

VATS- D PLEURAL PROCEDURES - OTHER

1 Decortication for empyema

2 Pneumothorax surgery (pleural symphysis +/- closure of air leak)

3 Other pleural procedures

VATS- E CHEST WALL/DIAPHRAGMATIC PROCEDURES

1. Correction of pectus deformity (code Nuss/MIRPE in "thoracoscopic" column) 2 Resection of primary chest wall tumour (not lung cancer)

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4 Minor

VATS- F MEDIASTINAL PROCEDURES

1 Thymectomy for thymoma

2 Thymectomy for myasthenia gravis

3 Throidectomy

4 Resection of other mediastinal mass/tumour 5 Mediastinoscopy / mediastinotomy

6 Other mediastinal proceudure

VATS- G OESOPHAGEAL/GASTRIC PROCEDURES

1 Oesophago-gastric resection - malignant

2 Oesophago-gastric resection - non-malignant

3 Other major oesophagogastric

4 Exploration only by any route for inoperable tumour

5 Minor oesophagogastric

VATS- H TRACHEAL SURGERY (includes carinal resection)

1 Tracheal resection - tumour

2 Tracheal resection - non-tumour

VATS- I OTHER PROCEDURES

1 Major

2 Minor

Z Endoscopic Procedures (Not VATS)

1 Therapeutic bronchoscopy

2 Therapeutic oesophagoscopy

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5,6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	5,6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	5,6
		(*e*) Describe any sensitivity analyses	6

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5,6
		(b) Give reasons for non-participation at each stage	5,6
		(c) Consider use of a flow diagram	5,6,14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5,6,7
		(b) Indicate number of participants with missing data for each variable of interest	5,6,7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7,8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7,8
		(*b*) Report category boundaries when continuous variables were categorized	7,8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7,8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.