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# Atrial Fibrillation after gastrointestinal surgery: incidence and associated risk factors

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**Authorship contributions:** MJL, JL & MW were responsible for project inception; all authors were involved in protocol design; EGH, and MJL were involved in data extraction and all authors were involved in writing of the paper. MJL, TMD and MB performed the statistical analysis.

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## **Abstract**

### **Background**

Atrial fibrillation is a common dysrhythmia which can occur following major physiological stress including surgery (post-operative AF). There are few data on post-operative AF following abdominal surgery. We set out to define the incidence of de novo post-operative AF following abdominal surgery, and associated risk factors.

### **Methods**

The Patient History Integrated Datastore administrative database was interrogated for patients aged  $\geq 65$  undergoing abdominal surgery from April 2012 - April 2014. Patients with pre-existing AF were excluded. The primary outcome was diagnosis of AF.

### **Results**

2,967 cases were included of whom 187 developed post-operative AF within 90 days (6.3%). The rate of post-operative AF varied by operation and was highest in small bowel resection (17.2%) and lowest in biliary surgery (4.8%). Median time to detection of post-operative AF was 32 days. Patients who developed post-operative AF were significantly older than those who did not develop AF (median age 75.3 years vs 72.4 years,  $p < 0.01$ ). Logistic regression modelling found increasing age (OR 1.03 (CI 1.01-1.06), hypertension (OR 1.73 (CI 1.19-2.51)), Congestive Cardiac Failure (CCF) (OR 3.04 (CI 1.88-4.92) and vascular disease (OR 2.29 (CI 1.39-3.37)) were predictive of the development of post-operative atrial fibrillation within 30 days. The area under the curve for this model was 0.733.

### **Conclusions**

Post-operative AF affects a significant number of patients following abdominal surgery. Demographics such as history of cardiovascular disease might aid prediction of post-operative AF. Post-operative AF is mostly identified following discharge, suggesting the need for post-operative screening.

Keywords: Atrial fibrillation, general surgery, risk factors

## **Introduction**

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting an estimated 1.1 million people in the United Kingdom (UK), with a prevalence of 4.7% in those aged >65 years [1,2]. As the prevalence of AF in the UK has increased over the last decade, partly due to the aging population, this condition has become increasingly important [3]. AF increases the risk of thrombo-embolic events, such as stroke and is associated with increased overall mortality in surgical patients [4,5].

AF is well documented following cardiac surgery with an incidence of between 20.8% and 27% and associated in-hospital and long-term mortality [6,7]. However, research investigating post-operative AF in general surgery, particularly in abdominal surgery, is less extensive. A recent review found that AF occurs following abdominal surgery in approximately 12-15% of patients [8]. New AF can be associated with a complication of surgery, such as an “anastomotic leak” or pelvic collection, or with other cardiovascular or respiratory complications, however, some patients develop atrial fibrillation without an obvious underlying complication[8,9]. Clinically significant new on-set AF is associated with longer hospital length of stay [9] and increased risk of stroke within 30 days (odds ratio 3.51 CI 1.45-8.52) [10].The pathophysiology of post-operative AF is thought to be multifactorial– the post-operative inflammatory response, sympathetic drive, atrial stretch and electrolyte disturbance interacting with a ‘vulnerable’ atrial substrate which triggers disorganised fibrillatory activity within atrial myocytes [11,12]. This differed from cardiac surgery where arrhythmogenesis is thought to arise from direct manipulation of heart or pulmonary vessels [13].

A systematic review by our team found that new post-operative AF occurs with an incidence of 10.9%. This varied with operation, affecting 17.6% of patients undergoing oesophagectomy, involving the thorax, compared to 7.6% in non-oesophageal surgery. Risk factors for the development of post-operative AF were identified including increasing age, history of cardiac disease and post-operative complications [8]. Given the population prevalence of AF, it is possible that surgery may precipitate an arrhythmia which might not have otherwise occurred. The included studies were heterogeneous, generally small, observational studies without

extended screening for pre-operative AF. Furthermore, none of the studies were designed for the reporting of prognostic factors.

The primary aim of this study was to define the incidence of new-onset AF following abdominal surgery, in a hospital population, identified by an administrative database. The secondary aim was to identify prognostic factors for the development of new-onset post-operative AF using baseline risk factors (i.e. those present prior to surgery, and unrelated to surgery). This study is classified as a stage II prognostic factor study within the Medical Research Council PROGNosis RESEARCH Strategy (PROGRESS) framework[14,15].

### **Methods**

This study was conducted with a pre-defined protocol and has been reported in line with the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement [16].

Data were extracted from the Patient History Integrated Datastore (PHInD) at Sheffield Teaching Hospitals. This database is populated using demographics of patients using the hospital services, linked ICD and OPCS codes, which are captured through clinical coding by administrators at end of care events (e.g. clinic or hospital discharge), or extracted from linked computer systems. This database can be searched on any combination of fields and bespoke reports produced. Data were extracted from this database on 22/06/2017. Local governance approvals were secured (project reference number 8022). All patients aged  $\geq 65$  undergoing abdominal surgery at STH between April 2012 and April 2014 were included. Patients were followed up in the dataset until the date of data extraction. Our sample was restricted to this age group due to the well-established correlation between AF and increasing age.

The abdominal surgery population consisted of gastrointestinal and hepatobiliary surgery, defined by their Operation and Procedure Codes (OPCS) Classification of Interventions and Procedures (version 4) codes, as detailed in appendix 1. Both laparoscopic and open procedures were included.

Demographic variables collected included age, sex, the presence of congestive cardiac failure (CCF), hypertension, diabetes mellitus, stroke, transient ischaemic attack (TIA), vascular disease, CHA<sub>2</sub>DS<sub>2</sub>VAS<sub>C</sub> score [17] and operation. Patients with a diagnosis of AF or atrial flutter prior to surgery were excluded.

The primary outcome was post-operative diagnosis of AF within 30 days. Secondary outcomes were post-operative diagnosis of AF within 90 days, long-term survival and identification of factors associated with the development of post-operative AF. The 10<sup>th</sup> edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes were used as detailed in appendix 2. Validation of the ICD-10 code for AF has shown 98% accuracy, 96% specificity and 98% sensitivity [18].

### **Statistical Analysis**

Descriptive analysis of demographics and the cumulative incidence of AF were calculated for the whole population and each operative subgroup. Time to diagnosis of atrial fibrillation was recorded. Candidate baseline factors (i.e. those existing prior to surgery) identified through a previous study [8] were assessed for relationship with post-operative AF were entered into a forward logistic regression model to assess their relationship with atrial fibrillation diagnosed within 30 days of surgery. Effect size was expressed as odds ratio (OR) with 95% confidence interval. Long-term survival was calculated and graphed on a survival curve and odds ratio of mortality was calculated using a log-rank test. A receiver operator curve (ROC) was plotted to assess the performance of the test using SPSS statistical software (IBM, Armonk, NY). Statistical significance was set at  $p \leq 0.05$  a priori.

### **Results**

Following interrogation of the database, 3124 cases were returned of which 157 were excluded; 153 patients had a diagnosis of AF prior to April 2012 and 4 patients underwent vascular procedures. Therefore 2967 patients were included in the analysis (see figure 1). Median follow-up was 941 days with a maximum follow-up period of 1907 days (0 day follow up relates to patients who died on the day of surgery). The characteristics of the study population are presented in table 1.

Of the 2967 patients without a pre-operative arrhythmia, 145 (4.9%) patients were diagnosed with new onset post-operative AF within 30 days and this rose to 187 (6.3%) at 90 days. The median time to diagnosis of AF was 32 days, however this varied significantly by age ( $p < 0.01$ ) as shown in figure 2. For patients 65-75, 75-85 and  $>85$  years, median time was 28, 40 and 29 days respectively (figure 2). Development of AF within 90 days post-operatively was associated with a significantly increased risk of long term all cause mortality (OR 1.78 (CI 1.33-2.39)  $p < 0.001$ ) (figure 3).

The incidence of post-operative AF varied by procedure type, with the highest rates of post-operative AF seen following upper gastrointestinal resection, colorectal resection and small bowel resection at 15.5%, 13.9% and 17.2% respectively. Biliary surgery, pancreatic resection and benign upper gastrointestinal surgery had the lowest rates at 4.8%, 5.2% and 5.6% respectively (figure 4).

The patients who developed post-operative AF were significantly older with a median age of 75.3 years (Interquartile range (IQR) 70.9-80.6) compared to 72.4 years (IQR 68.5-77.9) in those who were not diagnosed with POAF ( $p < 0.01$ ). The incidence of post-operative AF increased as age increased: 7.9% (6.8-9.3), 12.6% (10.7-14.9) and 17.9% (13.1-24.1) in patients aged 65-75, 75-85 and  $>85$  years respectively. The incidence of post-operative AF was higher in males (13.4%) than females (9.13%) (Fishers exact test,  $p < 0.01$ ). There was no difference in CHA<sub>2</sub>DS<sub>2</sub>VASc [17] between the post-operative AF and No-AF group (median 3 vs 3,  $p = 0.09$ , Mann Whitney U test).

Operation type and putative baseline factors of age, sex, CCF, hypertension, vascular disease, diabetes mellitus, and previous stroke were entered into a logistic regression model for risk factors related to onset of AF within 30 days of surgery. The analysis found increasing age (OR 1.03 (CI 1.01-1.06), hypertension (OR 1.73 (CI 1.19-2.51)), CCF (OR 3.04 (CI 1.88-4.92) and vascular disease (OR 2.29 (CI 1.39-3.37)) were predictive of the development of post-operative atrial fibrillation. The included characteristics are presented in table 2. Receiver operator curve was

plotted for the proposed prognostic model, and area under the curve was calculated as 0.733, showing moderate performance (figure 5).

## **Discussion**

This study has shown that approximately 6% of patients over the age of 65 will develop new onset AF within 90 days of abdominal surgery and this patient group have a significantly lower long-term survival. It also identified age, history of heart failure, hypertension and vascular disease, as factors which predict an increased risk of developing this complication.

The major strength of this study is the large number of cases assessed, with long post-operative follow up available. This has demonstrated that the development of AF does not happen solely in the immediate post-operative period but that the incidence continues to increase until 30 days post-operatively, the point when complications are classically attributed to surgery [19,20]. The incidence continues to rise until 90 days post-operatively. Therefore, AF may develop following discharge, suggesting the need for post-operative assessment or screening. Although we showed that there is a significant difference in long-term survival between those that did and did not develop post-operative AF this could be related to confounding factors as those with AF are also more likely to be older or have underlying cardiovascular disease. This was also all-cause mortality so could include unrelated complications.

This study has allowed us to identify potential risk factors for the development of post-operative atrial fibrillation to allow proposal of a prognostic model. The definition of post-operative could be challenged as the median time to diagnosis of AF is 32 days. This remains a valid study as this is typically the time to diagnosis of symptomatic AF as routine screening was not carried out. It is plausible that the onset of AF may have therefore been closer to surgery. This cannot be confirmed without prospective screening of patients.

We identified age, history of heart failure, hypertension and vascular disease as associated with post-operative AF. Most of these factors also predict the presence of AF outside the setting of surgery, because they result in atrial structural changes,



including dilation and fibrosis, resulting in a vulnerable atrial myocardium [21]. Others have attempted to identify factors associated with post-operative AF, albeit in non-cardiac thoracic surgery. Increasing age, male sex, and CCF have been identified as risk factors [20,22], as has baseline heart rate [23]. Baseline brain natriuretic peptide (BNP) has also been proposed as a potential predictive tool for post-operative atrial fibrillation [24]. Whilst the American Association of Anaesthesiologists (ASA) score was available, we decided not to assess the performance of this as a prognostic factor. ASA is related to a global assessment of the patient, and may not discriminate purely on cardiovascular factors. It is also a subjective estimate or measure, and as such could be 'gamed' in a prognostic model.

The limitations of this study are inherent in its design. Data from administrative coding is known to have a degree of inaccuracy [25] and is not comprehensive in recording factors such as post-operative complications. This may be reflected in the recording of outcomes in this study. As a tertiary centre, our unit provides specialist services across a geographic region which includes district general hospitals. The study is limited by its single centre nature and it may be possible that those developing atrial fibrillation or stroke following surgery sought care from their general practitioner or their local hospital, in which case their outcomes will be missing in our system. We have other concerns related to baseline screening for atrial fibrillation. Pre-operative assessment routinely performs a 12-lead echocardiogram (ECG) on patients over the age of 65 – this may not capture baseline paroxysmal AF. This may lead to incorrect estimations of incidence in this population. Despite these concerns, our reported incidence is broadly in line with the literature [8]. These concerns and limitations could be addressed in a prospective multi-centre cohort study.

This is, necessarily, part of a larger body of work. This study identifies and quantifies potential risk factors for post-operative atrial fibrillation in a historic cohort and in a single centre. This model should be tested in a multi-centre prospective cohort. This cohort should have robust baseline assessment for pre-existing atrial fibrillation and estimation of true post-operative event rate with screening ECG's up to 90 days to identify an accurate rate of post-operative AF. The study should be designed to identify baseline prognostic factors for post-operative AF, as well as the independent

effect of post-operative complications on risk assumptions. The short term outcomes of post-operative AF including both inpatient and outpatient health resource use must also be determined. This may pave the way for a stratified medicine trial in prophylaxis of post-operative atrial fibrillation in a high-risk group following abdominal surgery.

### **Conclusions**

Post-operative atrial fibrillation affects around 6% of patients undergoing abdominal surgery. Increasing age, male sex hypertension, vascular disease and congestive cardiac failure are characteristics with potential prognostic value in the development of post-operative atrial fibrillation.

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**Table 1: Summary of patient demographics**

**Table 2: Factors entered in logistic regression model to predict AF within 30 days of surgery**

**Table 3: Cases of AF diagnosed within 30 days and 90 days post-operatively, presented by operation**

**Figure 1: Flow chart to show coding of interventions**

**Figure 2: Time to diagnosis of post-operative atrial fibrillation by age bracket**

**Figure 3: Survival curve to show long-term mortality of patients developing AF within 90 days post-operatively**

**Figure 4: Point estimates of rates of AF by type of operation, presented with 95% confidence intervals**

**Figure 5: ROC Curve demonstrating performance of predictive model. Area under curve = 0.733**

**Appendix 1: OPSC codes used to define gastrointestinal and hepatobiliary**

**surgery**

**OPCS**

**Code**

**Operation**

G01	Excision of oesophagus and stomach
G03	Partial excision of oesophagus
G04	Open extirpation of lesion of oesophagus
G05	Bypass of oesophagus
G06	Attention to connection of oesophagus
G10	Open operations on varices of oesophagus
G11	Open placement of prosthesis in oesophagus
G27	Total excision of stomach
G28	Partial excision of stomach
G29	Open extirpation of lesion of stomach
G30	Plastic operations on stomach
G31	Connection of stomach to duodenum
G32	Connection of stomach to transposed jejunum
G33	Other connection of stomach to jejunum
G34	Artificial opening into stomach
G35	Operations on ulcer of stomach
G36	Other repair of stomach
G38	Other open operations on stomach
G58	Excision of jejunum
G59	Extirpation of lesion of jejunum

G60	Artificial opening into jejunum
G61	Bypass of jejunum
G62	Open endoscopic operations on jejunum
G69	Excision of ileum
G70	Open extirpation of lesion of ileum
G71	Bypass of ileum
G74	Creation of artificial opening into ileum
G75	Attention to artificial opening into ileum
H01	Emergency excision of appendix
H04	Total excision of colon and rectum
H05	Total excision of colon
H06	Extended excision of right hemicolon
H07	Other excision of right hemicolon
H08	Excision of transverse colon
H09	Excision of left hemicolon
H10	Excision of sigmoid colon
H11	Other excision of colon
H12	Extirpation of lesion of colon
H13	Bypass of colon
H14	Exteriorisation of caecum
H15	Other exteriorisation of colon
H29	Subtotal excision of colon
H30	Other operations on colon
H33	Excision of rectum
H34	Open extirpation of lesion of rectum



H35	Fixation of rectum for prolapse
H47	Excision of anus
J02	Partial excision of liver
J03	Extirpation of lesion of liver
J04	Repair of liver
J05	Incision of liver
J18	Excision of gall bladder
J19	Connection of gall bladder
J27	Excision of bile duct
J28	Extirpation of lesion of bile duct
J29	Connection of hepatic duct
J30	Connection of common bile duct
J32	Repair of bile duct
J33	Incision of bile duct
J55	Total excision of pancreas
J56	Excision of head of pancreas
J57	Other partial excision of pancreas
J62	Incision of pancreas
T30	Opening of abdomen

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**Appendix 2: ICD codes used to define outcomes**

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<b>ICD Code</b>	<b>Outcome</b>
G45	Transient cerebral ischaemic attacks and related syndromes
I48	Atrial fibrillation and flutter
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Other nontraumatic intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
K59	Cardioverter defibrillator introduced through the vein

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### **Appendix 3: Grouping of OPCS Procedures used for analysis**

<b>Group</b>	<b>OPCS Procedures</b>
Benign upper GI	G05: Bypass of oesophagus
	G06: Attention to connection of oesophagus
	G10: Open operations on varices of oesophagus
	G11: Open placement of prosthesis in oesophagus
	G30: Plastic operations on stomach
	G31: Connection of stomach to duodenum
	G32: Connection of stomach to transposed jejunum
	G33: Other connection of stomach to jejunum
	G35: Operations on ulcer of stomach
	G36: Other repair of stomach
	G38: Other open operations on stomach
	G61: Bypass of jejunum
	G62: Open endoscopic operations on jejunum
	G71: Bypass of ileum
	Biliary
J19: Connection of gall bladder	
J27: Excision of bile duct	
J28: Extirpation of lesion of bile duct	
J29: Connection of hepatic duct	
J30: Connection of common bile duct	
J32: Repair of bile duct	
J33: Incision of bile duct	

Colorectal resection	H01: Emergency excision of appendix
	H04: Total excision of colon and rectum
	H05: Total excision of colon
	H06: Extended excision of right hemicolon
	H07: Other excision of right hemicolon
	H08: Excision of transverse colon
	H09: Excision of left hemicolon
	H10: Excision of sigmoid colon
	H11: Other excision of colon
	H12: Extirpation of lesion of colon
	H29: Subtotal excision of colon
	H47: Excision of anus
	H33: Excision of rectum
	H34: Open extirpation of lesion of rectum
Gastrostomy formation/revision	G34: Artificial opening into stomach
Liver resection	J02: Partial excision of liver
	J03: Extirpation of lesion of liver
	J04: Repair of liver
	J05: Incision of liver
Other colorectal	H13: Bypass of colon
	H35: Fixation of rectum for prolapse
	H30: Other operations on colon
Pancreas resection	J55: Total excision of pancreas
	J56: Excision of head of pancreas
	J57: Other partial excision of pancreas

	J62: Incision of pancreas
Small bowel resection	G58: Excision of jejunum
	G59: Extirpation of lesion of jejunum
	G69: Excision of ileum
	G70: Open extirpation of lesion of ileum
Stoma formation/revision	G60: Artificial opening into jejunum
	G74: Creation of artificial opening into ileum
	G75: Attention to artificial opening into ileum
	H14: Exteriorisation of caecum
	H15: Other exteriorisation of colon
Upper GI resection	G01: Excision of oesophagus and stomach
	G02: Total excision of oesophagus
	G03: Partial excision of oesophagus
	G04: Open extirpation of lesion of oesophagus
	G27: Total excision of stomach
	G28: Partial excision of stomach
	G29: Open extirpation of lesion of stomach

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GI = gastrointestinal