Duration and magnitude of postoperative risk of venous thromboembolism after cholecystectomy: a population based cohort study

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ABBREVIATIONS

GP – General Practitioner

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

VTE – Venous Thromboembolism

ABSTRACT

Background:

This study aimed to identify burden and risk of VTE associated with cholecystectomy in England.

Methods:

An historical cohort study of cholecystectomy patients from 2001-2011 was undertaken using linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care data. Crude rates and adjusted hazard ratios (HRs) were calculated for risk of VTE following cholecystectomy using Cox regression.

Results:

24 677 patients were identified with a rate of VTE in the first year following cholecystectomy of 2.80 per 1000 person years (95% CI 2.18-3.59). Patients aged >/=70 vs aged <50 had 8.3-fold increase in risk of VTE (HR 8.27, 95% CI 3.72-18.35); patients with BMI >30 vs BMI <30 had 2.4-fold increase in risk (HR 2.42, 95% CI 1.40-4.18); open vs laparoscopic operation had 3-fold increase in risk (HR 2.94, 95% CI 1.55-5.55). Compared to general population, VTE risk was highest in the first 30 days post-operatively with 9.9-fold risk following emergency cholecystectomy and 4.5-fold risk after inpatient cholecystectomy (HR 9.90, 95% CI 4.42-22.21; HR 4.54, 95% CI 2.85-7.21).

Conclusions:

Cholecystectomy is associated with a low absolute risk of VTE we have identified high risk groups including the elderly, obese and those having open surgery.

INTRODUCTION

Over 66 000 cholecystectomies are performed each year in England at a cost of around £111.6 million[1]. The majority of these are performed laparoscopically, allowing early ambulation and reduced length of hospital stay which should decrease the risk of VTE [2]. However it has been proposed that the laparoscopic approach could paradoxically increase the risk of VTE due to pneumoperitoneum induction, activation of the coagulation system and the historically longer duration of procedure [3]. Current studies reporting the risk of VTE associated with cholecystectomy are not population based and much of the data from these studies are no longer contemporary [4-10]. These studies focus on the inpatient period only or follow up to 30 days only, relying on either secondary care data or surveillance methods and therefore may not reflect true rates of clinically important VTE [3, 11].

Little is known regarding the timescale of VTE risk following cholecystectomy and no studies have stratified their follow-up period to address this. Additionally, it has not been established if variation in the risk of VTE occurs between emergency (surgery during same admission as emergency presentation), elective (admission on elective basis for surgery) or day-case admissions (admission and discharge on same day as surgery). A prior population based study reported 90 day rates of VTE using linked primary and secondary data however no description of risk by individual procedure type was reported[12]. Persson et al investigated bleeding and VTE risk following cholecystectomy using the Swedish Register of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks) to identify cholecystectomies from 2005 to 2010. They reported that VTE prophylaxis was associated with increased bleeding risk but with no reduction in VTE risk[13]. However the population studied may not be generalisable to practice in other countries as they did not report whether elective procedures were day case or inpatient, and no association with obesity was reported. In that particular study, pharmacological VTE prophylaxis was prescribed based on the individual surgeons' risk assessment, rather than defined risk criteria. Identifying

those patients at high risk of VTE and the time period at risk would allow targeted thromboprophylaxis to minimise the risk of VTE whilst preventing an excess risk of bleeding events [14].

This study aimed to identify the burden, timing and risk factors for VTE associated with cholecystectomy in England using population-based, linked primary and secondary care data from England. This study also aimed to identify specific sub-groups with increased risk of VTE to target for consideration of prophylaxis.

MATERIAL AND METHODS

Patients and data sources

This study used data from two linked health care databases which we have described in detail previously [15, 16]. In brief the Clinical Practice Research Datalink (CPRD) contains diagnostic and prescription data coded using Read codes[17] for approximately 3.4 million active patients. CPRD has been linked to Hospital Episodes Statistics data (HES) which contains a detailed record for each 'episode' of admitted patient care delivered in England, either by NHS hospitals or delivered in the independent sector but commissioned by the NHS. Records are coded using a combination of International Statistical Classification of Disease and Related Health Problems (ICD-10) for primary diagnosis at discharge along with Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4 (OPCS 4) detailing procedures performed. The anonymised patient identifiers from CPRD and HES were linked by a trusted (anonymous) third party by using the National Health Service (NHS) number, date of birth, postcode, and sex. Most patients were matched exactly according to NHS number (over 90% of patients are linked in this way), with the remaining patients linked probabilistically on the basis of postcode, date of birth, and sex. We also used death certificate data from the Office for National Statistics (ONS).

Cohort Identification

The cohort was identified from CPRD-HES linked data using OPCS codes for cholecystectomy (Codes J181, J182, J183, J184, J185, J188, J189). A laparoscopic approach was confirmed by the inclusion of an OPCS code for laparoscopy Y508, Y571 and Y752. Follow up was until development of a VTE event, death, leaving a participating GP practice or 31st Dec 2011, whichever was earliest. Those under the age of 18 years were excluded as we have reported the data previously [18].

The population cohort was identified from the CPRD-HES linked data. In order to maximize statistical power, all available controls without a diagnosis of surgery during their CPRD-HES record were eligible. The population cohort were drawn from a larger study of all patients undergoing gastrointestinal surgery in which they were frequency matched in a ratio of 10:1 by 5-year-age bands to those undergoing surgery. They received a pseudo-diagnosis date generated at random between the study start and end date (2001-2011).

Outcome Definition

VTE diagnosis was determined from medical codes in the CPRD and HES (using Read and ICD-10 respectively). These were considered to be a VTE event if supported by either: a prescription for an anticoagulant or other evidence of treatment in an anticoagulation clinic (such as a medical code) between 15 days before and 90 days after the VTE diagnosis, or a date of death within 30 days of the event. Additionally, an underlying cause of death of VTE was included as evidence of VTE diagnosis. Only the first confirmed instance of VTE was included in the analysis. We took the date of diagnosis of VTEs to be the episode start date for VTEs occurring within the same hospital spell as the index operation. Participants were excluded if they had a VTE prior to admission for cholecystectomy. The definition using primary care data alone has been validated previously showing 84% of cases were valid[19] and used in our prior studies of VTE[20, 21].

Exposures

Comorbidity was determined from the CPRD and HES data and classified using the Charlson index prior to admission for surgery and categorised as no comorbidity, 1 comorbidity or 2 or more comorbidities[22]. Body mass index (BMI) was defined from the primary care data and classified as less than 30 kg/m^2, greater than or equal to 30 kg/m^2 or missing. Finally, admission type was defined as in-patient, emergency or day case based on the type of admission recorded for the surgical procedure.

Statistical Analysis

First, we described the basic characteristics of our cohort using frequencies and percentages. Median ages were calculated and compared using Kruskal Wallis Test. Absolute rates of VTE (per 1000 person years) were calculated for the first year following surgery. These rates were then stratified by age, comorbidity, BMI and admission type. The impact of these factors on VTE risk was assessed in terms of Hazard ratios (HR) using a Cox regression model compared to the baseline group for each category. The post discharge period was further stratified into individual months up to 3 months. Cox regression analysis was again used to provide HRs for each time interval at risk comparing risk of those undergoing in-patient, emergency or day case cholecystectomy compared to the general population. Missing data was fitted as a separate category in all analyses. All data management and analysis were performed using Stata 14 (Statacorp, Texas 77845 USA).

The study had approval from the Independent Scientific Advisory Committee approval board which provides scientific advice to the Medicines and Healthcare products Regulatory Agency (MHRA) (Protocol 11-051R).

RESULTS

Demographics of cohort

We identified 24 677 people undergoing a cholecystectomy with the majority having their operation as an inpatient electively (76.9%; 18 975/24 677) (Table 1). Of those having a cholecystectomy, 76.9% (18 975/24 677) were female. The median age at operation was 53 years (inter quartile range (iqr) 40-65 years) compared to 52 years (iqr 38-65) in the population cohort. Those undergoing in-patient and emergency cholecystectomy had higher levels of comorbidity than those undergoing day case surgery (Table 1). The median length of stay following an inpatient procedure was 1 day (iqr 1-3 days) compared with a median of 7 days (iqr 4-11 days) for an emergency procedure. Laparoscopic cholecystectomy was undertaken in 97.6% (3156/3234) of day case procedures, 89.1% (16 910/18 975) of inpatient elective procedures and 73.6% (1817/2468) of emergency procedures. In total 84.4% (20 829/24 677) of procedures were undertaken for cholelithiasis and 13.6% (3354/24 677) for acute cholecystitis.

Absolute rates of VTE following cholecystectomy

The overall rate of VTE in the first year following cholecystectomy was 2.80 per 1000 person years (95% CI 2.18-3.59) (Table 2). The rates of VTE increased with increasing age, peaking in patients aged 70 and over (absolute rate of 8.00 per 1000 person years (95% CI 5.52-11.58)). This represented an adjusted 8.3-fold increase in overall VTE risk compared to patients aged under 50 years (HR 8.27, 95% CI 3.72-18.35) (Table 2) and there was evidence that this increase was linear across the age groups ($p<0.001$).

Absolute rates of VTE were higher in patients with obesity compared to patients without obesity (3.81 per 1000 person years (95% CI 2.68-5.42) *vs* 2.00 per 1000 person years (95% CI 1.33-3.01). This increase represented an adjusted 2.4-fold risk of developing VTE

post-operatively compared to patients with a BMI under 30 (HR 2.42, 95% CI 1.40-4.18) (Table 2).

The absolute rate of VTE was lower in laparoscopic procedures compared to open procedures (2.19 per 1000 person years (95% CI 1.62-2.95) *vs* 9.25 per 1000 person years (95% CI 5.47-15.61)). This represented an adjusted 3-fold increased risk of VTE for open procedures compared to laparoscopic (HR 2.94, 95% CI 1.55-5.55) (Table 2).

The absolute rate of VTE following day case surgery was low (1.47 per 1000 person years). There was no-significant increase in risk of VTE following emergency or in-patient surgery when accounting for other factors.

Relative risk of VTE following cholecystectomy by mode of surgery compared to the general population

When compared to the general population, absolute rates of VTE following cholecystectomy were highest in the first month following surgery. Those having an emergency cholecystectomy had the highest absolute rate (31.65 per 1000 person years (95% CI 14.22 – 70.45) *vs* 3.16 per 1000 person years in the general population (95% CI 2.87 – 3.49)). This represented an adjusted 9.9-fold VTE risk following emergency cholecystectomy (HR 9.90, 95% CI 4.42-22.21) compared to the general population (Table 3). Those having inpatient procedures also had higher absolute rates of VTE than in the general population (absolute rate 12.87 per 1000 person years (95% CI 8.21-20.18) *vs* 3.16 per 1000 person years (95% CI 2.87 – 3.49)). This represented an adjusted 4.5-fold risk of developing VTE (HR 4.54, 95% CI 2.85-7.21). No VTE events were recorded in day-case patients in the first month following surgery (Table 3).

DISCUSSION

Summary of findings

Absolute rates of VTE following cholecystectomy are low. However, we found increasing age, obesity and open operations all carried an increased relative risk of VTE. The risk of VTE was highest in the first month after surgery, particularly following emergency admission, with a 9.9-fold VTE risk following emergency cholecystectomy in the first month post-operatively compared to the general population. The absolute rates returned towards the population level in the second month following surgery.

Limitations and strengths of study

This study used linked healthcare data to identify patients undergoing cholecystectomy from population-based data, with identification of operative procedures from secondary care along with the definition of VTE in a validated manner from primary and secondary care, therefore it is uniquely placed to quantify VTE risk reasonably accurately[19]. The identification of VTE in these patients relies on the clinical suspicion of their practitioner and subsequent referral for investigation, thus minimising surveillance bias that may occur in patients identified solely in hospital, as has been suggested in other studies[11]. Using linked prescription data allowed a validated measure of clinically significant VTE events, giving a good representation of clinical VTE burden. This study detected symptomatic VTE only rather than using surveillance measures that would identify clinically silent events. As such the true rates of VTE may be higher than reported in the present study findings. An important limitation of this study is that the data available did not contain detail about pharmacological or mechanical prophylaxis that was prescribed in hospital. No data on prescription or use of mechanical prophylaxis was available in the present study, therefore we are unable to

comment on its importance. However, previous reports have suggested that many patients at risk of VTE are not prescribed any pharmacological prophylaxis while in hospital [23, 24].

The present study contains data from 2001 to 2011. It should be noted that the current guidance was published in 2010, and as such the data from before this period may not reflect current best practice [2, 25]. Nevertheless, current guidance does not define patients groups with higher risk, nor does it offer guidance on the timing of risk. The present study aimed to clarify these aspects of VTE risk in relation to cholecystectomy.

Other literature

Previous work by Sinha et al identified characteristics of patients undergoing cholecystectomy using HES data [26]. The population identified in the present study showed similarities with regard to gender (76.9% female *vs* 76.1%female), age (median age 53 *vs* mean age 52), proportion undergoing emergency procedures (10.0% (2468/24677) *vs* 12.5%) and proportion converted from laparoscopic to open (4.5% (1104/24677) *vs* 5.0%). However, our population had more co-morbidities recorded with 16.8% (4154/24 677) of patients with a Charlson score of 2 or more (compared to 2.5%) and 60.7% (14 967/24 677) of patients with a Charlson score of 0 (compared to 83.1%). This difference is likely due to improved recording in the current study, given the availability of primary care data and the completeness of comorbidity recording, compared to the reliance on secondary care data in the Sinha study[19].

Bouras et al also analysed linked primary and secondary care data for 90 days following general surgical procedures and reported symptomatic VTE in 0.3% of patients overall after cholecystectomy, which is in line with our estimate (0.25%)[12]. However they did not report on the associated risk factors or timing of events for cholecystectomy, limiting their results in application to clinical decision-making. Stromberg et al described symptomatic VTE in 0.25% of post-cholecystectomy patients overall. They also found increased risk in over 70s

and with open cholecystectomy. These findings are supported by the present study. However the data used were from the Swedish Register of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography, were followed for only 30 days and it is not stated whether elective procedures were performed as inpatient or day case [7].

Age has previously been shown to be associated with increased risk of VTE following cholecystectomy. In this study an 8.3-fold increase in overall VTE risk was seen in patients aged over 70 years compared to patients aged under 50 years. Using measurement of coagulation factors pre- and post- laparoscopic cholecystectomy, it has been suggested by Garg et al that age may be an important risk factor for activation of coagulation, theoretically increasing the risk of VTE, although no actual VTE events were recorded in their study [27]. Indeed, Stein et al reported the prevalence of VTE after laparoscopic cholecystectomy increased from 0.17% in patients aged 21 to 30 years to 0.90% in patients aged 71 to 80 years, similar to our findings[28]. White et al reported a steady increase in the incidence of VTE with increasing age in cholecystectomy[8]. Both of these studies used data from the USA and used only secondary care rather than prescription-validated data.

Obesity has also been suggested as a risk factor for hypercoagulability, and therefore a subsequent VTE risk, following cholecystectomy [27]. In the present study, obesity was found to be associated with increased risk of VTE with a 2.4-fold increased risk of VTE compared to patients with a BMI under 30 kg/m^2. Other studies have also reported increased incidence of DVT or PE following open cholecystectomy, as supported by the present data, which demonstrate higher VTE risk after open cholecystectomy compared to laparoscopic[5-7, 10, 29]. This may be due to early ambulation and shorter inpatient period stay facilitated by undergoing laparoscopic compared to open cholecystectomy [2].

In the present study, we have identified the first 30 days as the highest risk period. There is little information available regarding timing of symptomatic VTE events following

cholecystectomy in other literature. Many studies used surveillance methods to detect VTE within days to weeks of cholecystectomy although this included clinically silent VTE [4, 5, 30]. Other studies using routinely collected data followed patients for 30 days only and used only secondary care data[7, 13]. Three studies reported overall VTE rate at 90 and 91 days but failed to further identify variation in risk over this time period[8, 10, 12].

Clinical Significance

While cholecystectomy in general is a low risk procedure for VTE, this study has identified certain groups of patients who have increased risk of developing VTE. This includes patients who are obese, elderly or who undergo open procedures. These groups of patients should therefore be considered for pharmacological VTE prophylaxis as VTE risk may outweigh the bleeding risk. However the majority of patients following cholecystectomy are at low risk of VTE and therefore do not warrant routine extended thromboprophylaxis beyond the inpatient period. More work is needed to identify the bleeding risk associated with pharmacological thromboprophylaxis in these higher risk groups to guide decision making for inpatient or extended pharmacological thromboprophylaxis. Using data from the present study, no conclusions regarding use of mechanical thromoboprophylaxis can be made therefore the authors are unable to make recommendations on its use.

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Table 1. Demographics of those undergoing cholecystectomy by method of admission and population controls.

	General Population		Day case		Elective		Emergency	
	No.	%	No.	%	No.	%	No.	%
Gender								
Male	787,484	47.1	634	19.6	4,373	23	695	28.2
Female	884,065	52.9	2,600	80.4	14,602	77	1,773	71.8
Age								
>/=18-49	711,922	42.6	1746	54.0	7544	39.8	1081	43.8
50-59	287,821	17.2	730	22.6	4,222	22.3	432	17.5
60-69	299,473	17.9	572	17.7	3,943	20.8	405	16.4
>/=70	372,333	22.3	186	5.8	3,266	17.2	550	22.3
Comorbidity								
0	1,080,906	64.7	2,204	68.2	11,440	60.3	1,323	53.6
1	292,780	17.5	690	21.3	4,248	22.4	618	25
>/=2	297,863	17.8	340	10.5	3,287	17.3	527	21.4
BMI (kg/m^2)								
<30	1,000,395	59.8	1,728	53.4	9,787	51.6	1,214	49.2
>/=30	286,511	17.1	1,183	36.6	7,061	37.2	956	38.7
Missing	384,643	23	323	10	2,127	11.2	298	12.1
Laparoscopic								

Yes			3,156	97.6	16,910	89.1	1,817	73.6
No			77	2.4	1,176	6.2	437	17.7
Converted			1	0	889	4.7	214	8.7

Table 2. Rates of VTE in patients undergoing cholecystectomy.* corrected for all other variables in table and admission type.

		Absolute Rates				Univariate Cox Model		Multivariate Cox M	
		Events	Time	Rate	95% CI	HR	95% CI	HR	95% C
Gender	Male	17	5.01	3.36	2.09-5.41	ref		ref	
	Female	45	17.08	2.63	1.97-3.53	0.78	0.45-1.37	1.16	0.65-2.(
Age (years)	>/=18-49	9	9.29	0.96	0.50-1.86	ref		ref	
	50-59	9	4.9	1.84	0.96-3.53	1.89	0.75-4.77	1.95	0.77-4.9
	60-69	16	4.45	3.60	2.20-5.87	3.70	1.64-8.38	3.78	1.64-8.1
	>/=70	28	3.5	8.00	5.52-11.58	8.17	3.85-17.31	8.27	3.72-18.
BMI	<30	23	11.5	2.00	1.33-3.01	ref		ref	
	≥30	31	8.13	3.81	2.68-5.42	1.90	1.11-3.27	2.42	1.40-4.1
	Missing	8	2.51	3.18	1.60-6.38	1.59	0.71-3.56	1.93	0.86-4.3
Comorbidity	0	30	13.58	2.21	1.55-3.16	Ref		ref	
	1	15	4.94	3.04	1.83-5.04	1.37	0.74-2.55	1.06	0.57-1.9
	≥2	17	3.62	4.70	2.92-7.56	2.12	1.17-3.85	1.07	0.57-2.(
Laparoscopic	Laparoscopic	43	19.63	2.19	1.62-2.95	Ref		ref	
	Open	14	1.51	9.25	5.47-15.61	4.20	2.30-7.67	2.94	1.55-5.5
	Converted	5	0.99	5.05	2.10-12.14	2.29	0.91-5.78	1.53	0.60-3.9

*adjusted for gender, age, comorbidity, BMI

Table 3. Rates of VTE by mode of admission over follow-up period.

			Univariate		Multivariate*	
	Rates of VTE (per 1000 person years)	95% CI	HR	95% CI	HR	95% CI
1st Month						
General population	3.16	2.87-3.49	ref		ref	
Day Case	0		0		0	
In-patient	12.87	8.21-20.18	4.07	2.57-6.44	4.54	2.85-7.21
Emergency	31.65	14.22-70.45	10.00	4.47-22.40	9.90	4.42-22.21
2nd Month						
General population	3.04	2.75-3.35	ref		ref	
Day Case	0		0		0	
In-patient	4.64	2.21-9.74	1.53	0.72-3.23	1.66	0.79-3.52
Emergency	5.24	0.74-37.19	1.73	0.24-12.28	1.66	0.23-11.84
3rd Month						
General population	2.71	2.43-3.02	ref		ref	
Day Case	4.04	0.57-28.67	1.49	0.21-10.61	2.43	0.34-17.33
In-patient	0		0		0	
Emergency	5.36	0.76-38.16	1.98	0.28-14.12	1.89	0.27-13.50

*adjusted for gender, age, comorbidity, BMI