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Reporting Bias Leading to Discordant Venous Thromboembolism Rates in the United States Versus Non-US Countries Following Radical Cystectomy: A Systematic Review and Meta-analysis

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Abstract

Context—Postcystectomy bladder cancer (BCa) patients are at high risk for developing venous thromboembolism (VTE). The literature varies widely in the reporting of VTE in this population.

Objective—To determine the VTE rate in subjects undergoing radical cystectomy (RC) and highlight specific factors affecting this rate.

Evidence acquisition—This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database, registration number: CRD42015016776. We queried MEDLINE, the Cochrane Library, Embase, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. Search terms captured BCa, RC, and VTE. Per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, abstracts were reviewed for inclusion/exclusion criteria by two reviewers, and disagreements were resolved by a third reviewer. A search of the gray literature and references of pertinent articles was also performed. The date of our last search was December 15, 2014. For

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unreported data, authors were contacted. Data were abstracted in duplicate and pooled using a random effects (RE) model. Subgroup analyses and meta-regression were performed to determine risk factors for VTE.

Evidence synthesis—We identified 2927 publications, of which 223 met inclusion criteria for this review. A total of 1 115 634 surgeries were performed on patient population (80% men) with a total of 51 908 VTEs. The VTE rate estimated by the RE model was 3.7%. Due to significant heterogeneity, subgroup and meta-regression analyses were undertaken. These revealed a higher rate of VTE in US studies at 4.49% compared with “westernized” non-US studies at 3.43% and “nonwesternized” non-US based studies at 2.50%. Other important modifiers included minimally invasive surgery at 5.54% versus open surgery at 3.55%, and age. The case-fatality rate of pulmonary emboli was 44%.

Conclusions—VTE is common in patients undergoing RC. Reporting of VTE is heterogeneous and the rate varies according to study-level factors, including surgery type and country of origin. Limitations of this study include the preponderance of observational studies in the final analysis and lack of complete reporting of all variables of interest within each study.

Patient summary—In this review, we determined the venous thromboembolism (VTE) rate in postsurgical bladder cancer patients. VTE events did vary significantly among certain subgroups.

Keywords

Bladder cancer; Cystectomy; Deep venous thrombosis; Pulmonary embolism; Venous thromboembolism

1. Introduction

Cancer is a well-known risk factor for thrombotic events. Venous thromboembolism (VTE) includes pulmonary embolism and deep vein thrombosis, and is the most common form of malignancy-associated thrombosis. Arterial thrombosis and systemic thrombotic syndromes (eg, disseminated intravascular coagulation) can also occur. Previously published data report 2% of bladder cancer (BCa) patients will experience a VTE event within 2 yr of diagnosis, a probability that is five times higher than the overall population [1–3]. When VTE occurs in a patient with BCa, it is associated with a threefold increased risk of death [1,2]. The rate of VTE changes significantly depending on patient-specific characteristics such as age, disease stage, and modality of treatment. However, once a VTE event occurs, the prognostic weight it carries is independent of these patient-specific factors [4].

BCa is considered among the high-risk cancers for development of VTE [5]. Interestingly, radical cystectomy (RC) has been shown to confer a 2.1-fold increase in the risk of VTE compared with muscle-invasive bladder cancer patients who did not undergo the procedure [5]. This is unique when compared with other surgically treated malignancies such as breast, lung, and colorectal cancers, as their risk of VTE decreases significantly after surgical excision of the tumor [1,6–8]. The increased risk of VTE seen in BCa likely has a multifactorial etiology and risk factors include complex pelvic surgery, extended lymphadenectomy, prolonged time in the lithotomy position, and biochemical alterations in the coagulation cascade known to occur in BCa [4]. However, to date, there has never been a

systematic review of the published literature to determine the overall rate of VTE in surgical BCa patients.

Our objective in this study was to systematically amass all relevant publications to estimate the overall rate of VTE in adult patients undergoing RC for BCa and the study-level factors affecting this rate.

2. Evidence acquisition

2.1. Protocol registration and search strategy

Our protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) registry (CRD42015016776). An experienced information specialist searched MEDLINE, the Cochrane Library, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science through August 2014 with no limit on the earliest date. We used MeSH terms, Emtree terms, CINAHL headings, and keywords as search terms, and we combined specific terms for urinary bladder neoplasms, venous thrombosis, and bladder surgery, according to our inclusion criteria. We limited electronic searches to *humans* and *English*. Exact search strings can be found in Supplementary Table 1. All citations were imported into an electronic database and, to minimize retrieval bias, we also used semiautomatic manual searches of reference lists of pertinent articles, using the Scopus citation database. To identify relevant “gray literature,” ClinicalTrials.gov, the National Cancer Institute's clinical trial database, PROSPERO, and COS Conference Papers Index were also searched [9].

2.2. Eligibility criteria

To be eligible, retrieved articles had to (1) describe a surgical treatment for BCa and (2) report a VTE rate (either explicitly or calculable). No article was excluded on the basis of method of analysis or perceived quality/bias, since such assessments are subjective and lack reproducibility [9–12]. Studies that dealt primarily with animals, pediatric patients, RC performed for reasons other than BCa, or subgroups with known coagulopathies were excluded. Duplicate publications and case reports were also excluded.

2.3. Manuscript screening and data abstraction

Two reviewers independently assessed study abstracts for eligibility, with disagreements adjudicated by a third reviewer. The full text of eligible abstracts was obtained and reviewed whenever possible. Variables of interest were abstracted into an electronic data capture form. In cases where variables were missing or unreported in the study manuscript, we attempted to contact study authors for this information. Authors were e-mailed twice, each followed by a 2-week response period, after which further response was deemed unlikely and missing data for the study considered unrecoverable. The primary end point of interest was the overall VTE rate, which included both pulmonary emboli (PE) and deep venous thrombosis (DVT) events, expressed as a summary proportion of VTE events divided by the total number of subjects at risk. Secondary end points were the DVT rate, PE rate, mortality rate from PE, and the PE case-fatality rate (ie, patients who died from PE). Studies missing both

the primary end point (VTE) and key secondary end points (DVT or PE) were excluded from further analysis.

2.4. Statistical methods

For the primary and secondary end points, fixed effects and random effects (RE) models were constructed for pooling proportions. For variance stabilization, proportions were pooled after arcsine transformation [13], and restricted maximum likelihood estimation was used to calculate the between-study variance (τ^2) in the RE models [14]. Pooled arcsine-transformed proportions and their 95% confidence intervals (CIs) were then back-transformed to the normal scale for presentation. The presence of residual heterogeneity was assessed using the I^2 statistic and tested using the Cochran Q test [15]. Since we hypothesized that the VTE rate would vary from study to study, the RE model was used in all subgroup analyses and meta-regressions.

To determine if any individual study was an outlier or had significant influence on the pooled results, we examined externally standardized residuals, DFFITS values, DFBETAS values, Cook's distances, and covariance ratios [16]. Additionally, we performed a jackknife sensitivity analysis (ie, leave-one-out analysis) of all our models. Due to a large amount of unexplained heterogeneity in our primary outcome between studies, we conducted subgroup analyses and mixed-effects meta-regression models to explore possible sources of heterogeneity, using prespecified subgroups. Subgroup moderator variables were tested for significance in the meta-regression models by using the Knapp-Hartung method (without truncation) as well as the Higgins-Thompson permutation test [17,18]. Moderators measured on a continuous scale were analyzed as such in meta-regression models but presented categorically for easier interpretation. Last, we assessed the possibility of publication bias using the Begg-Mazumdar rank correlation test [19], the Egger regression test [20], and by assessing funnel plots before and after Duval-Tweedie trim-and-fill [21]. All analyses were performed using R v.3.1.2 with packages *meta* and *metafor* installed [22–24].

3. Evidence synthesis

3.1. Search results

Our initial search resulted in 2123 publications, following de-duplication. After title and abstract review, 642 publications were reviewed in full. We also identified eight additional articles from the gray literature that were included in our analysis. The authors were contacted for further data from 78 papers, which garnered 30 responses, and the desired data from 14. Ultimately, we abstracted variables of interest from 223 publications that included data on a total of 1 115 634 patients (Fig. 1) [25]. A full summary of the included studies can be found in Supplementary Table 2.

3.2. Pooled event rate, heterogeneity, and subgroup analyses

The pooled VTE event rate and the distribution of event rates across studies are shown in Figure 2. The event rates for all five end points following RC are shown in Table 1, and all were highly significant by the Cochran Q test. We explored this heterogeneity by performing subgroup analyses to determine if we could identify study-level factors affecting VTE (Table

2). Three study-level factors were identified that potentially influenced the overall VTE event rate: study country of origin ($p = 0.001$), cystectomy technique (open vs minimally invasive, $p = 0.044$), and patient age ($p = 0.054$).

3.3. Meta-regression

A meta-regression model was then created for cystectomy patients and included age, country of origin, and cystectomy technique, and was fit to 180 component studies that had information on all three moderators. This showed that, after adjusting for all moderators, the only study-level factor that significantly affected the VTE event rate was country of origin. Table 3 shows some predictions from the model. The inclusion of the three moderators in the meta-regression model significantly reduced I^2 from 86.8% to 80.9%, indicating that while the model did explain some between-study variability, a large amount of residual heterogeneity remained.

3.4. Influence analysis

Using the RE model for the primary end point, we identified four studies that were potentially outliers: Clement et al [26], Kauffman et al [27], Maurer et al [28], and Witherington et al [29]. However, in jackknife sensitivity analysis, stepwise removal of these studies only minimally affected the overall pooled event rate (the maximum change in event rate was 0.063%), indicating that the RE pooling was fairly insensitive to these potential outliers (Supplementary Fig. 2). With respect to heterogeneity, the maximum reduction in I^2 was 3%, seen with the deletion of the study by Reese et al [30]. Given the very high level of residual heterogeneity that remained after the exclusion of any individual study and that the RE model seemed insensitive to outlying and/or influential studies, no studies were excluded from our analyses for influence or outlier reasons.

3.5. Publication bias

The Duval-Tweedie test, the Begg-Mazumdar rank correlation test, and the Egger regression test were all highly significant at $p < 0.001$, again suggesting some publication bias was present. Examination of standard funnel plots and Duval-Tweedie trim-and-fill funnel plots suggested that studies with high VTE rates were more likely to be published than studies with low VTE rates (Fig. 3, Supplementary Fig. 3). The implication of this publication bias is that the pooling of the published literature may over- or underestimate the true rate of VTE in the postcystectomy population.

3.6. Discussion

Cystectomy remains the gold standard for treatment of invasive and/or refractory BCa, and with it comes the potential for significant morbidity. The risk for developing complications following this procedure is multifactorial. The physical health of the patient population who typically develops BCa, the complexity of the surgery, and, perhaps, some biochemical changes in the systemic milieu all contribute to the morbidity of this operation. VTE is of substantial importance to those who treat BCa regularly. In this meta-analysis, we found that in those undergoing RC, the rate of VTE is 3.7%, which is several-fold greater than the general population and similar to the VTE rate in patients with colorectal cancer, with a

reported 2-yr cumulative incidence of 3.1% [8,31]. While the PE rate after bladder surgery is only 1.6%, we found that 44% of those who experience it will die. This PE case-fatality rate is significantly greater than that of the general population, in which the case-fatality rate is approximately 15%, depending on patient-specific factors [31–34]. Therefore, although PE is an uncommon occurrence, it carries an alarming fatality rate in the postcystectomy period.

Interestingly, we found a substantial difference in the reported VTE rate between studies based in the United States and those based in other countries. There appears to be a dose effect with increasing reported VTE rates, depending on the level of westernization of the study's country of origin. There are several possible explanations for this difference. First, there may be something fundamentally different between BCa patients in the United States such as the Western diet, obese population, or some unknown environmental factors. Second, surgery performed in the United States may differ systematically from that outside that country. For example, lymphadenectomies might occur more frequently or be of greater extent, longer operative times might be present, or less perioperative thromboembolic prophylaxis might be given. Third, there may be reporting bias such that studies not coming from the United States do not capture or report the true VTE rate. We feel that reporting bias is the most likely cause of this difference because of the change in reported VTE depending on how westernized the study's country of origin is.

The reader might wonder if a 1% absolute difference in VTE rates is of clinical consequence. If this meta-analysis were to be used to inform a randomized controlled trial of VTE prophylaxis after cystectomy (which the literature is lacking), the following scenario should be considered. Assuming a relative risk (RR) of 40% when using VTE prophylaxis (ie, a 60% RR reduction, similar to what is seen for VTE prophylaxis in major general surgical procedures) [35,36], we estimated the sample size required across a range of baseline cystectomy VTE rates (ranging from 1% to 5%) (Supplementary Fig. 4). If the baseline VTE rate was 2.7% (1% below our estimate), the study would require 1108 patients, whereas if the baseline VTE rate was 4.7% (1% above our estimate), the study would require 627 patients. The difference in the sample size (and budget) between these two scenarios is nearly twofold, which would be highly relevant for the trialist. A second scenario to consider is a hypothetical population of 1000 patients undergoing cystectomy with VTE rates that differ by just 1%. With a VTE rate of 2.7% and PE rate of 0.6% (each 1% lower than our estimates), we would expect 27 VTE events (RR = 0.77 vs our estimate) and 6 deaths from PE (RR = 0.43 vs our estimate). Conversely, with a VTE rate of 4.7% and PE rate of 2.6% (1% above our estimates), we would expect 47 VTE events (RR = 1.27 vs our estimate) and 26 deaths from PE (RR = 1.6 vs our estimate). This demonstrates that a small, 1% absolute difference in VTE can be associated with a RR that is large and clinically relevant for this disease state (Supplementary Table 3).

An interesting finding was that the rate of VTE in those undergoing minimally invasive RC was statistically greater than that of those undergoing open RC. This may be due to the typically longer operative time using minimally invasive techniques and extended period of sustained pneumoperitoneum [37]. Interestingly, of the 223 included studies, only 38 reported use of intraoperative DVT prophylaxis, and 31 reported postoperative prophylaxis. Given the extensive literature in support of perioperative VTE prophylaxis and guidelines

advocating its use, we found this quite surprising [38–40]. We conducted a subgroup analysis to pool the VTE rates in studies that reported intra- or postoperative prophylaxis and those who did not. Higher rates of VTE were seen in those who reported that they did not use prophylaxis and the lowest rates in those who reported that they did use VTE prophylaxis. These pooled rates must be viewed with the aforementioned reporting bias in mind.

This systematic review was limited by a number of factors that are typically found in this type of study. There was a paucity of high-quality studies such as randomized controlled trials and prospective cohorts, with the majority of studies being retrospective. Many of the studies we included did not report all of the variables of interest and, despite contacting the authors, few were able to provide us with more accurate data. It should be noted that only two manuscripts reported routine postoperative DVT screening by lower extremity ultrasound. Removal of these studies from the analysis conferred no appreciable change in the pooled DVT or PE rates, and the heterogeneity remained essentially unchanged. Another limitation was the language restriction to English language only. However, a recent study by Morrison et al found that limiting meta-analyses to English-language publications does not introduce significant bias [41].

4. Conclusions

VTE occurs in 3.7% of patients undergoing RC; when the event is a PE, the case-fatality rate is 44%. The VTE rate varied by two study-level factors: country of study origin and cystectomy technique. There appears to be a dose effect on VTE rate, with increasing VTE rates depending on the level of westernization of the study's country of origin. This discordance is likely due, in part, to the presence of reporting bias in the published literature leading to an underestimation of the true VTE rate in non-US-based studies. Standardized identification and reporting of complications after RC may help future studies assessing the true rate of VTE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take-home message

Venous thromboembolism occurs at a high rate in bladder cancer and carries an alarming fatality rate when the diagnosis is pulmonary embolus. The reported rate is higher in US-based than non-US based studies, with a dose-effect relationship with westernization.

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Fig. 1.
– Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart [25].

Fig. 2.

– Forest plot of 223 studies showing the pooled VTE event rate using both the fixed and random effects models.

CI = confidence interval; VTE = venous thromboembolism.

Fig. 3.
 – (a) Standard and (b) Duval-Tweedie trim-and-fill funnel plots suggesting studies with higher rates of venous thromboembolism were more likely to be published.
 RE = random effects.

Table 1

Pooled thromboembolic event rates for subjects undergoing surgery for bladder cancer

Event type	Random effects		Heterogeneity			Studies, no.
	Event rate, %	95% CI, %	τ^2	I^2 , %	95% CI, %	
VTE	3.7	3.31–4.16	0.0048	97	95.8–97.6	223
DVT	2.1	1.68–2.51	0.0047	85	82.8–87.1	131
PE	1.6	1.40–1.89	0.0017	70	64.7–74.6	150
Death from PE	0.4	0.21–0.55	0.0017	52	38.1–62.8	81
PE case-fatality rate	44	37.2–51.1	0.0422	38	6.3–40.7	76

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE=venous thromboembolism.

Table 2

Subgroup analyses of factors affecting overall venous thromboembolism rates

Subgroup	Studies, no.	Patients, no.	Events, no.	Random effects model		p value	I ² , %
				Event rate (%)	95% CI		
Country of origin							
USA	98	1 057 606	51 211	4.49	3.89–5.13		
Non-USA, western	78	14 975	529	3.43	3.02–3.86	<0.001	95.7
Non-USA, other	47	43 053	168	2.50	1.89–3.21		
Year of publication	223						
1975				3.87	2.55–5.44		
1985				3.82	2.86–4.91		
1995				3.77	3.16–4.44	0.839	96.7
2005				3.73	3.31–4.17		
2015				3.68	3.12–4.29		
Trial type							
Prospective	75	9 280	420	3.74	3.02–4.54	0.162	96.8
Retrospective	147	1 106 327	51 486	3.12	2.67–3.60		
Study type [*] , no.							
Single center	176	46 994	1736	3.90	3.42–4.41	0.151	96.5
Multiple centers	47	1068 640	50 172	3.19	2.44–4.04		
Cystectomy technique							
Open	177	103 855	3549	3.55	3.12–4.01		
MIS	28	41 661	2376	5.54	3.97–7.36	0.044	89.8
Open and MIS	14	39 818	2279	4.32	2.72–6.26		
Continient diversion, %	161						
0				3.47	2.75–4.26		
25				3.48	2.96–4.04	0.921	75.7
50				3.50	3.06–3.97		

Subgroup	Studies, no.	Patients, no.	Events, no.	Random effects model		p value	I ² , %
				Event rate (%)	95% CI		
75				3.52	2.97–4.11		
100				3.53	2.78–4.38		
Male patients, %	184						
0				4.77	2.47–7.77		
25				4.33	2.74–6.27		
50				3.92	2.99–4.96		89.5
75				3.53	3.09–4.00		
100				3.15	2.48–3.90		
T2+ proportion, %	101						
0				2.95	1.23–5.39		
25				3.10	1.83–4.68		
50				3.24	2.48–4.10		70.2
75				3.39	2.82–4.01		
100				3.54	2.50–4.75		
Intraoperative prophylaxis							
Yes	35	16 336	921	4.22	3.30–5.25		
No	3	271	17	5.48	3.46–7.93	0.030	96.7
Not reported	185	1 099 027	50 970	3.12	2.71–3.55		
Postoperative prophylaxis							
Yes	28	19,071	1023	4.55	3.56–5.66		
No	3	271	17	6.29	4.04–9.00	0.006	96.6
Not reported	192	1 096 292	50 868	3.08	2.69–3.51		
Age, yr	183						
45				2.07	0.95–3.61		
55				2.73	1.95–3.64	0.054	88.3
65				3.48	3.07–3.92		
75				4.32	3.41–5.34		

Subgroup	Studies, no.	Patients, no.	Events, no.	Random effects model		p value	I ² , %
				Event rate (%)	95% CI		
85				5.24	3.45–7.39		

MIS = minimally invasive surgery.

* In the multicenter studies, there was no crossover between non-US countries and the United States in the included studies.

Table 3

Mixed effect meta-regression model predictions for venous thromboembolism

Age, yr	Country of origin	Cystectomy technique	Event rate, %	95% CI
65	Non-US	Open	2.9	2.44–3.50
		MIS	4.4	2.95–6.14
	US	Open	3.9	3.17–4.66
		MIS	5.5	3.89–7.44

CI = confidence interval; US = United States.