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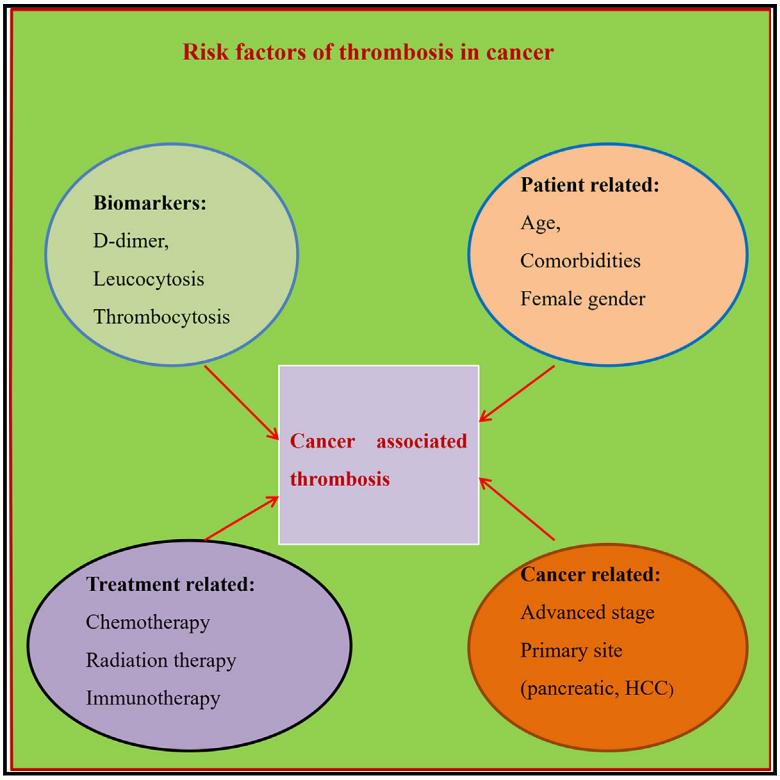
Magnitude of cancer-associated thrombosis in Africa: A systematic review and meta-analysis

Graphical abstract



Highlights

- Cancer-associated thrombosis becomes significant public health burden in Africa
- Age, comorbid disease, and high level of D-dimer are associated with increased risk of CAT
- Capacity-building programs on the prevention, diagnosis, and management of CAT are essential
- Evidence-based, multidisciplinary approach to care guidelines for CAT is essential

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In brief

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Magnitude of cancer-associated thrombosis in Africa: A systematic review and meta-analysis

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SUMMARY

Comprehensive data on the epidemiology of cancer-related thrombosis in Africa has been sparse until recently. Thus, this review was aimed to investigate the magnitude of cancer-related thrombosis in Africa. To obtain key articles, comprehensive search was conducted using various databases. A random-effects model was used to determine the pooled magnitude. Heterogeneity across the studies was checked, and publication bias was determined. The pooled magnitude of thrombosis among cancer patients in Africa is 11.65% (95% confidence interval [CI]: 9.02–14.28). Advanced age, comorbidity, and level of D-dimer were the factors associated with cancer-associated thrombosis.

Cancer-related thrombosis has become a significant public health burden in Africa. About 3 out of 25 cancer patients are at increased risk of acquiring thrombosis. It is better to provide training and capacity-building programs for healthcare providers in Africa on the prevention, diagnosis, and management of cancer-related thrombosis and develop standardized evidence-based multidisciplinary approach care guidelines.

INTRODUCTION

Cancer is becoming a growing burden for various lower- and middle-income countries, particularly in Africa and Asia.[1] According to the World Health Organization (WHO), it is the leading cause of morbidity and mortality worldwide, more pronounced in young adults and adolescents.[2] Recent data estimates suggest that the worldwide prevalence of cancer will be projected to increase by 47% in the year 2040 compared to the year 2020.[3]

Despite technological advancements in cancer treatments, leading to improved outcomes for patients, they still experience distressing life events. One of the most commonly encountered conditions is cancer-associated thrombosis (CAT), which is showing an increasing trend over time.[4] The current actual magnitude of cancer related thrombosis has been underrated.[5] Evidence shows that the magnitude of CAT has been increased by 3-folds in the last two decades.[6]

The risks of acquiring thrombosis among cancer patients were 2- to 20-fold higher than that of the general population without cancer.[7] Currently, 20% of the overall prevalence rate of thrombosis was related to active cancer.[8]

The development of cancer-related thrombosis is a multifactorial process, influenced by various risk factors from different domains including cancer-related, treatment-related, and patient-related factors.[9] High risk of thromboembolism also results from specific types of cancer, including lung, pancreatic, colorectal, and gynecological cancers (such as ovarian and cervical).[10] Studies have shown that time since cancer diagnosis, advanced stages, and the presence of distant metastasis contribute to the highest rates of thrombosis.[11] In addition, evidence has linked an increased risk of CAT to the presence of comorbidities, older age, a prior history of thrombosis, hereditary thrombophilia, and prolonged immobility.[12] Major surgery, chemotherapy, a central venous catheter, immunotherapy, and hormonal therapy are also associated with a high incidence of CAT.[13,14] Furthermore, several studies have identified that the causal correlation between cancer and thrombosis is complex, in which cancer cells have the potential to induce inflammation, vascular damage, and an increased production of procoagulant factors such as tissue factors, which stimulate the coagulation cascade and lead to thrombosis.[15]

Thromboembolism in cancer patients resulted in gruesome health outcomes. It is the leading premature cause of cancer-related morbidity and mortality.[16] It is also associated with poor treatment compliance, a declining quality of life, and decreased resilience.[17] Research results from Scandinavia show that CAT had a 3.4-fold higher risk of mortality as compared to cancer patients without it, regardless of cancer type and stage.[18] In addition, the extra economic burden of

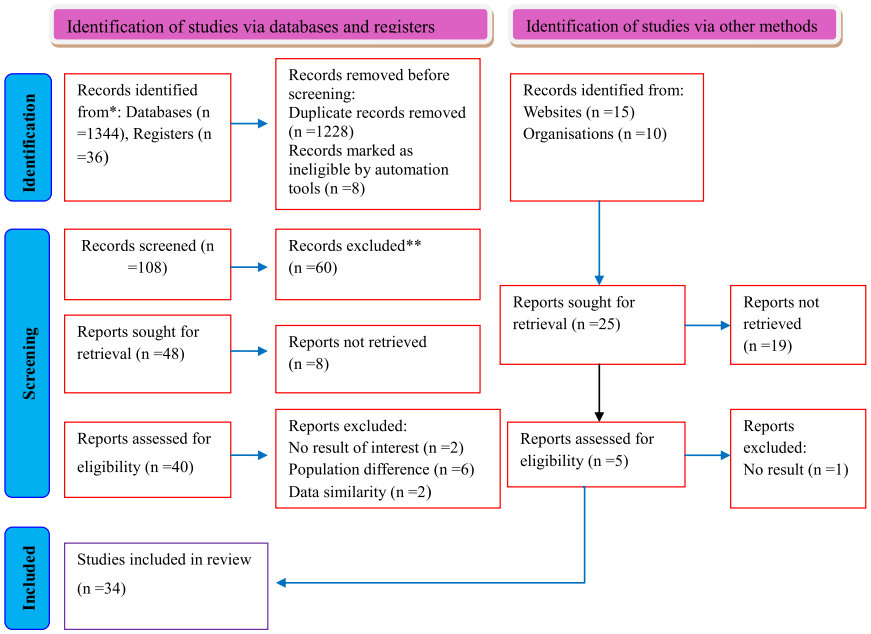

Figure 1. Prisma flow diagram showing the steps for screening the articles to be included

thrombosis in individuals with cancer is significant, given that CAT is associated with elevated health care resource utilization and health care expenses as compared with cancer patients without thrombosis.[19] The existing evidence identified that the annual average total cost for cancer patients with venous thromboembolism (VTE) was found to be almost 50% higher than that of cancer patients without VTE, and more than 60% of the total cost is related to inpatient care costs.[20] The burden of CAT extends beyond the physical and economic consequences; it is associated with significant psychological impacts such as social isolation, anxiety, and depression.[21]

There is a growing pool of data and research in this field of oncology in many parts of the developed world,[22] but data on the epidemiology of CAT in Africa have been sparse until recently. In Africa, CAT is becoming a significant public concern. There is a lack of standardized management protocol in most cancer treatment centers on the continent. The majority of these risky individuals were not screened, diagnosed, treated, or given appropriate prophylaxis.[23] Scholars suggest that healthcare professionals need to be equipped with the necessary skills to screen, diagnose, provide appropriate treatment, and prevent disease by identifying risk factors.[24] As a result, identifying the overall magnitude of CAT and its factors in Africa is critical for earlier intervention and treatment, ultimately leading to better outcomes and preventing negative impacts. Standardized policies and programs can be designed and implemented to maximize efficiency and effectiveness. Thus, this review was aimed to investigate the magnitude of CAT in Africa.

RESULTS

Literature search and identified results

Using various databases and repositories, a total of 1,405 articles were identified. From studies identified via databases and registries, 1,236 records were unrelated and ineligible with our outcome of interest and irrelevant and excluded before screening. Subsequently, reports of 73 articles were sought for retrieval, but 27 articles were not retrieved. The results of 45 articles were assessed for eligibility for inclusion. After reviewing the titles and abstracts of these articles, 11 of them were excluded. The full information in the remaining articles was comprehensively assessed. Finally, 34 articles were included in this review (Figure 1).

Description of included studies

This meta-analysis included 34 articles reporting the magnitude of CAT. Out of them, two articles were from Algeria,[25,26] six from Egypt,[27–32] seven from Ethiopia,[33–39] four from Uganda,[40–43] three each from Kenya[44–46] and Morocco,[47–49] two each from Nigeria[50,51] and South Africa,[52,53] and one each from Cameroon,[54] Gambia,[55] Rwanda,[56] Somalia,[57] and Togo,[58] respectively. Cumulative cohorts of 10,552 cancer patients participated in this study. Their ages range from 18 to 92. The minimum and maximum numbers of cancer patients who participated in the study reported per article were 17 and 2,500, respectively.[32,52] Regarding sex, about 33 articles reported the number of male and female cancer patients who participated in their study. Based on the evidence in these articles, the total number of cancer patients was 10,502, of which more than half (55%) were female cancer patients. The magnitude of thrombosis among cancer patients in Africa ranges from 0.6% to 45%, as reported in Uganda in different studies.[41,43] Among all identified cancer phenotypes, the leading cancer was breast cancer, which accounts for 13.25%, followed by hepatocellular carcinoma (6.72%), cervical (6.12%), colorectal cancer (6%), and bladder cancer (5.14%). Whereas brain, skin, melanoma, laryngeal, neuroendocrine, and multiple myeloma were the least cancer phenotypes in magnitude identified in this study (Table 1).

Magnitude of cancer-associated thrombosis

To estimate the overall magnitude of CAT in Africa, a random-effects model based on the DerSimonian-Laird method of analysis was used. This meta-analysis identified that the magnitude of thrombosis among cancer patients in Africa was 11.65%, with a 95% CI of 9.02–14.28, I^2 = 96.16%, and tau^2 = 53.32% (Figure 2). As a result, the test statistic revealed that there is a considerable level of heterogeneity. Before the final conclusion, the occurrence of significant heterogeneity among the studies should be addressed and explanations need to be established.

Table 1. Summary characteristics of the included studies for meta-analysis (*n* = 34)

Authors	Country	Cancer phenotype	Pub yr	Prevalence	Sample	Mean age	Study design	Quality score
Yabeyu et al.[33]	Ethiopia	Mixed	2020	10.2	423	43	Retrospective cross-sectional	10
Mkedder et al.[25]	Algeria	Solid	2021	9.65	114	58.7	Prospective cohort	9
Degu et al.[44]	Kenya	Solid	2022	3.5	231	49.2	Prospective cohort	9
Kefale et al.[34]	Ethiopia	Solid	2022	9.5	150	51.4	Retrospective cross-sectional	9
Nganou-Gnindjio et al.[54]	Cameroon	Mixed	2022	7.6	408	NR	Retrospective cross-sectional	9
Elsayed et al.[27]	Egypt	Solid	2022	11.2	214	51.6	Prospective cohort	8
Elsayed et al.[28]	Egypt	Hematological	2023	9.9	81	NR	Prospective cohort	8
Omar et al.[30]	Egypt	Mixed	2018	10	20	59.85	Prospective cross-sectional	8
Gamal et al.[32]	Egypt	Mixed	2017	22.8	2500	35	Cross-sectional	8
Ephrem et al[35].	Ethiopia	Hematological	2023	6.3	80	52	Retrospective cohort	9
Ahmed et al.[36]	Ethiopia	Mixed	2019	5.7	70	41.2	Retrospective cross-sectional	9
Admasu et al.[37]	Ethiopia	Solid	2023	6.8	250	42.5	Comparative cross-sectional	10
Amina et al.[45]	Kenya	Mixed	2018	10.9	266	50.25	Cross-sectional	8
Orangi et al.[46]	Kenya	Solid	2021	2.65	377	NR	Cross-sectional	9
Zayyan et al.[50]	Nigeria	Solid	2019	7.5	67	54.7	Prospective cross-sectional	8
Ayandipo et al.[51]	Nigeria	Solid	2023	1.2	167	46.00	Retrospective cross-sectional	8
Sewunet et al.[38]	Ethiopia	Mixed	2016	10.2	384	43.30	Retrospective cross-sectional	10
Tadege[39]	Ethiopia	Mixed	–	25	392	49.17	Case-control	10
Afassinou et al.[58]	Togo	Mixed	2023	6	1457	56.36	Retrospective cross-sectional	8
Clement et al.[40]	Uganda	Mixed	2021	10.8	111	52.40	Retrospective cohort	8
Kamombe-Zingwari et al.[52]	S/Africa	Mixed	2021	29.4	17	NR	Cross-sectional	9
Ndow et al.[55]	Gambia	Solid	2023	11.9	252	43	Prospective cohort	8
Mohamed et al.[57]	Somalia	Solid	2022	15.3	268	52.6	Retrospective cross-sectional	8
Mohamed et al.[26]	Algeria	Mixed	2022	6	165	65	Prospective cohort	10
Shiba[53]	S/Africa	Solid	2019	7.9	598	NR	Cross-sectional	8
Refaat et al.[29]	Egypt	Solid	2013	32.5	80	61	Prospective cross-sectional	9
Tohamy et al.[31]	Egypt	Solid	2021	6.6	456	57.7	Retrospective cross-sectional	10
Gamukama et al.[42]	Uganda	Solid	2021	6.1	98	48	Cross-sectional	8
Mboizi et al.[41]	Uganda	Solid	2023	0.6	180	NR	Cross-sectional	8
Mbabazi[43]	Uganda	Solid	–	45	200	NR	Cross-sectional	8
Mugeni et al.[56]	Rwanda	Mixed	2019	36	50	41	Retrospective cross-sectional	9
Messoudi et al.[49]	Morocco	Solid	2019	15	120	59.2	Cross-sectional	9
Kaddouri et al.[48]	Morocco	Mixed	2017	15.8	158	55.9	Retrospective cross-sectional	9
Nada et al.[47]	Morocco	Solid	2020	14.9	148	64	Retrospective cohort	9

It is necessary to perform subgroup analysis or meta-regression analysis based on study-level characteristics.[59]

Handling of heterogeneity

Subgroup analysis

To mitigate the occurrence of significant variability among and within the studies, subgroup analysis was performed by considering geographical region, country level, and cancer phenotype.

Regional and country level prevalence of cancer-associated thrombosis in Africa

The analysis done by considering geographical region found that the pooled magnitude of cancer-related thrombosis in Eastern Africa was 11.82% (95% CI: 7.99–15.65), the Northern part of Africa was 13.78% (95% CI: 8.45–19.10), Southern Africa was 15.83% (95% CI: −4.49 to 36.17), and Western Africa was 6.49% (95% CI: 3.20–9.78). As indicated earlier, the subgroup meta-estimation of Southern-African-based studies has statistically non-significant effects on the overall magnitude of cancer-related thrombosis. This reveals geographical region of the studies has an impact on the meta-analysis estimate because the socioeconomic status of each country is different. Each study article was also stratified based on the specific setting in which it was conducted. The subgroup meta-estimate revealed that the overall magnitude of thromboembolism among cancer patients in Egypt (15.28%) (95% CI: 6.89–23.66), Ethiopia (10.58%) (95% CI: 6.17–14.99), Algeria (7.24% (95% CI: 3.85–10.63), and Kenya (5.33% (95% CI: 1.36–9.30) has statistically significant effects on the overall pooled estimate. The effect estimates from Morocco (15.25%) (95%CI: 11.83–18.66) were not different from 0 at the 10% significant level. In contrast, the

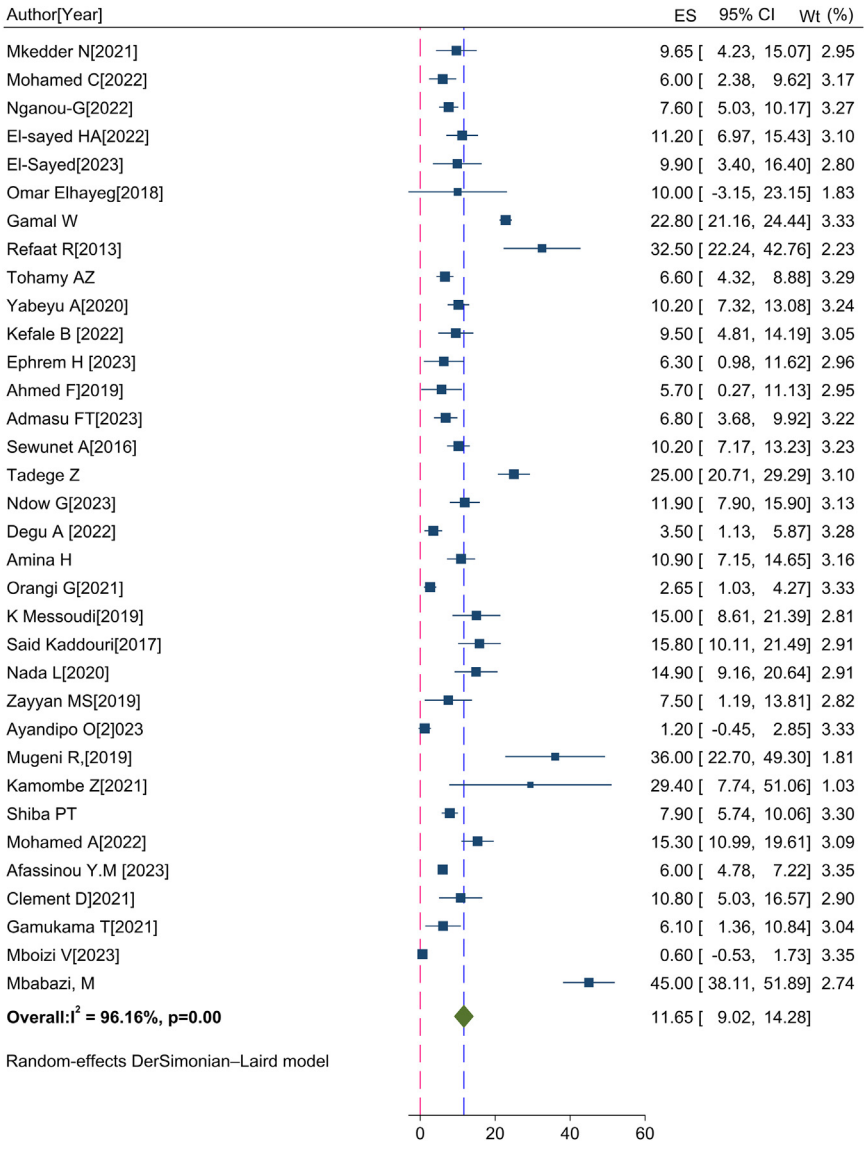

Figure 2. Forest plot of the pooled magnitude of cancer-related thrombosis in Africa

which suggests that the effect in this group is not significantly different from 0 at a 10% level of significance. Three studies[25,34,37] with a total of 514 colorectal cancer patients reported the magnitude of thrombosis. The meta-analysis revealed the overall pooled estimate of 8% (95% CI: 5.70–10.35), and the heterogeneity level of this group is 0.00%. This indicates that there is a statistically significant effect in this group at the 10% level of significance. Three studies,[47,55,57] which included 668 patients with hepatocellular carcinoma, identified the prevalence of thrombosis among them. The meta-analysis indicated a pooled estimated prevalence of thrombosis in patients with HCC was 13.78% (95% CI: 11.16–16.38). No heterogeneity was observed in this group. There was a statistically significant effect, as indicated by the given *p* value. Whereas, two studies[28,35] reported the prevalence of thrombosis among hematological cancer patients. The pooled estimate prevalence of thrombosis among hematological cancer patients were 7.74% (95% CI: 3.62–11.86). The meta-estimates of thrombosis from two studies[50,53] in cervical cancer were 7.86% (95% CI: 5.81–9.90). No heterogeneity was observed, and there was no statistically significant effect in either hematological or cervical cancer at 10% level of significance. Sixteen studies[26,27,29,30,32,33,36,38–40,45,48,52,54,56,58] that do not specify the specific cancer phenotype also reported the prevalence of thrombosis. The unclassified or mixed cancer group has the highest estimate, which is about 14.30% (95% CI: 10.09–18.49). This suggests that there is a statistically significant effect in these groups. The crude prevalence of thrombosis in each single study concerned with abdominopelvic,[43] breast, prostate and lymphoma,[44] bladder,[31] and pancreatic[49] cancer patients were 45%, 3.5%, 6.6%, and 15.0% respectively. The pooled prevalence of thrombosis for these cancer phenotypes is not reported, as a meta-analysis could not be performed due to an insufficient number of studies. Overall, it is clear that specific cancer phenotypes have an impact on the overall meta-estimate (Table 3).

subgroup estimate from Uganda (15.36%) (95% CI: −0.06 to 30.78), Nigeria (3.58%) (95% CI: −2.40 to 9.57), and South Africa (15.83%) (95% CI: −4.49 to 36.17) has no statistically significant effect on the overall meta-analysis result at the *p* value of 0.1. When the number of studies decreases, the subgroup heterogeneity decreases; for single studies, the level of heterogeneity might become zero. Because single studies are included from each country in Cameroon, Gambia, Rwanda, Somalia, and Togo, the level of heterogeneity in subgroups becomes zero, and as a result, their impact on the pooled estimate will not be different from zero at the given level of significance (Table 2).

Prevalence of thrombosis based on cancer phenotypes in Africa

Based on the specific cancer phenotypes, four studies[41,42,46,51] encompassing 822 breast cancer patients reported the prevalence of CAT. The overall pooled prevalence of thrombosis among breast cancer patients was 1.8% (95% CI: 0.32–3.28),

Meta regression

In spite of subgroup analysis, results resolved and identified the source of heterogeneity across the studies; we performed meta-regression to identify the association between the samples and

Table 2. Summary of subgroup analysis result of pooled estimates of cancer-related thrombosis

Covariates	Groups	Number of studies	Subgroup estimate	95% CI	Heterogeneity (I^2, p value of Q)
Region level	Eastern Africa	16	11.82	7.99–15.65	95.90, <0.001
	Northern Africa	11	13.78	8.45–19.10	94.54, <0.001
	Western Africa	5	6.49	3.20–9.78	89.69, <0.001
	Southern Africa	2	15.83	−4.49 to 36.17	73.32, =0.053
Specific country	Algeria	2	7.24	3.85–10.63	16.94, =0.273
	Cameroon	1	7.60	5.02–10.17	–
	Egypt	7	15.28	6.89–23.66	96.65, <0.001
	Ethiopia	7	10.58	6.17–14.99	89.09, <0.001
	Gambia	1	11.90	7.90–15.89	–
	Kenya	3	5.33	1.36–9.30	87.34, <0.001
	Morocco	3	15.25	11.83–18.66	0.00, =0.972
	Nigeria	2	3.58	−2.40 to 9.57	72.12, =0.058
	Rwanda	1	36.00	22.69–49.30	–
	South Africa	2	15.83	−4.49 to 36.17	73.32, =0.053
	Somalia	1	15.30	10.99–19.61	–
	Togo	1	6.00	4.78–7.21	–
	Uganda	4	15.36	−0.06 to 30.78	98.20, <0.001

specific cancer phenotypes with cancer-related thrombosis across the studies. The result showed that the coefficient estimate was 0.013 for samples. This implies that, for an increase of the sample by one cancer patient, the magnitude of cancer-related thrombosis increases by 0.013, making all other variables constant. In addition, by setting breast cancer as the reference category, the prevalence of thrombosis in hepatocellular cancer is 11.48 units higher than the average prevalence of thrombosis in cases of breast cancer. This indicates that HCC is significantly associated with a higher prevalence of thrombosis and that patients are at a significantly higher risk of thrombosis compared to those with breast cancer (Table 4).

Publication bias

The qualitative examination of the funnel plot indicated the presence of publication bias (Figure 3). However, Egger's linear regression test for potential asymmetry of the funnel plot shows no evidence of publication bias, nor was there evidence of small studies excessively impacting the overall estimated value, as indicated by a p value of 0.2392, which is greater than 0.05.

Factors associated with cancer-related thrombosis

As the presence of cancer increases the risk of developing thrombosis, this study identified various factors that contribute to the development of thrombosis among cancer patients: poor performance status,[33,54] level of D-dimer,[26,27] advanced age,[34,37,46] the presence of comorbidity,[34,37,39,42] larger tumor size, being overweight, and metastasis.[37] Certain cancer treatments, such as prolonged chemotherapy use, recent stage of surgery, and prolonged immobility[39,46] are among the factors that potentially increase the risk of developing thrombosis among cancer patients.

Table 3. Summary of pooled prevalence of thrombosis in specific cancer phenotypes

Cancer phenotype	Number of studies	Total cancer patients	Total number of CAT	Crude prevalence of CAT (%)	Pooled prevalence of CAT (%)	95% CI	I^2 (%) and p value
Abdomino-pelvic	1	200	90	45	N/A	N/A	N/A
BPL	1	231	8	3.5	N/A	N/A	N/A
Bladder	1	456	30	6.6	N/A	N/A	N/A
Breast	4	822	19	2.3	1.8	0.32–3.28	62.73, 0.045
CRC	3	514	32	6.23	8	5.70–10.35	0.00, 0.018
HCC	3	668	96	14.37	13.78	11.16–16.38	0.00, 0.049
Hematological	2	161	13	8.07	7.74	3.62–11.86	0.00, 0.401
Cervical	2	665	52	7.82	7.86	5.81–9.90	0.00, 0.906
Pancreatic	1	120	18	15.0	N/A	N/A	N/A
Mixed	16	6715	1023	15.23	14.30	10.09–18.49	95.78,<0.001
All types	34	10552	1381	13.10	11.65	9.02–14.28	96.16,<0.001

N/A, not applicable.

Table 4. Meta regression results on selected variable

Variable	Coefficient	Std.err.	Z	P>|Z|	[95%CI]
Sample	0.013	0.002	5.97	<0.001	0.01–0.02
Abdominopelvic	42.48	7.34	5.79	0.780	28.09–56.87
BPL	0.98	6.55	0.15	0.880	−11.86 to 13.83
Bladder	4.08	6.54	0.62	0.533	−8.74 to 16.92
Breast	**Ref.**	–	–	–	–
CRC	6.06	4.62	1.31	0.189	−2.98 to 15.12
HCC	11.48	4.64	2.47	0.013	2.38–20.57
Blood	5.50	5.44	1.01	0.312	−5.16 to 16.18
Cervical	5.21	5.26	0.99	0.322	−5.10 to 15.53
Pancreatic	12.48	7.22	1.73	0.084	−1.66 to 26.64
Others	11.29	3.36	3.36	0.071	4.69–17.89

Ref., reference.

Association of age- and cancer-related thrombosis

To determine the association between age- and cancer-related thrombosis, two studies reported age as a factor in CAT. The results of the meta-analysis indicate that the risk of thrombosis was nearly four times (odds ratio [OR] = 3.47, 95% CI = 2.73–4.21) higher among cancer patients of advanced age when compared with individuals of younger age (Figure 4).

Association of comorbidity conditions and cancer-related thrombosis

The likelihood of developing thrombosis among cancer patients was about five times higher (OR = 4.86, 95% CI = 3.45–6.27) among cancer patients with comorbidity (Figure 5). A significant level of heterogeneity was computed with no small-study effects, with an I^2 value of 88.06%, $p < 0.001$. To mitigate this level of heterogeneity, a sensitivity analysis was performed, which indicates that no single study excessively affects the overall estimates (Data S1). Egger's linear regression analysis indicates that there is no small-study effect (beta = 5.34, prob > |z| = 0.3240).

Association of level of D-dimer and cancer-related thrombosis

This review has tried to investigate the effects of the magnitude of the biomarker D-dimer on the risk of developing thrombosis among cancer patients. As a result, a statistically non-significant level of result was identified in which cancer patients with an increased D-dimer level were associated with three times an increased risk of developing thrombosis as compared with their counterparts (OR = 2.75, 95% CI: −0.65 to 6.15) (Figure 6).

DISCUSSION

Despite the advancement of comprehensive cancer treatment, cancer-related thrombosis is increasing over time and is the most prevalent comorbidity among patients.[60] It has been associated with an elevated risk of morbidity and mortality and varies according to the type and stage of the tumor as well as individual risk factors.[61] As far as we know, the pooled figure of cancer-related thrombosis in Africa has not yet been determined. As a result, this systematic review and meta-analysis investigated an overall pooled estimated magnitude of thrombosis in cancer patients in Africa. It also identified the overall magnitude of cancer-related thrombosis across different cancer phenotypes, countries, and regions of the continent. The result showed that the overall estimated magnitude of thrombosis among cancer

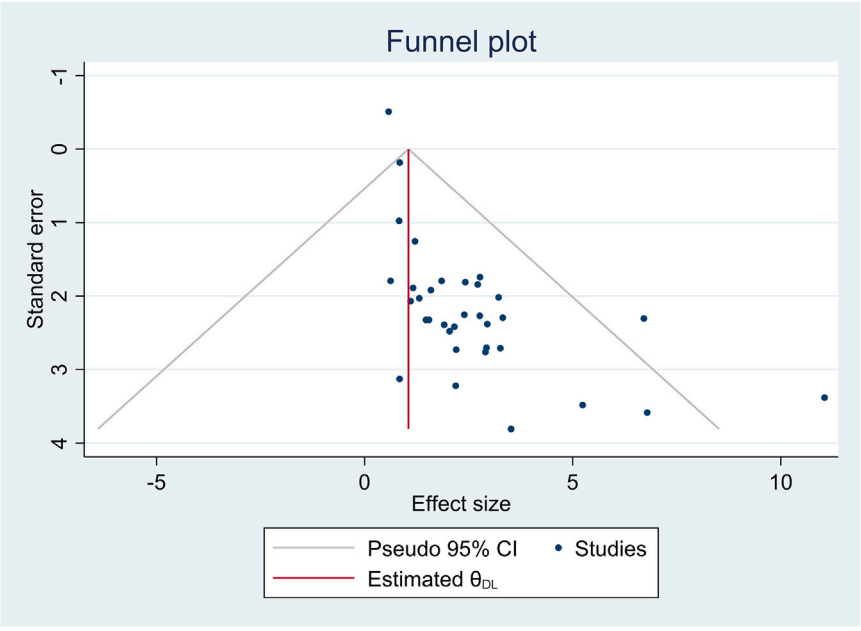

Figure 3. Meta-funnel plot of the magnitude of cancer-related thrombosis among cancer patients in African region

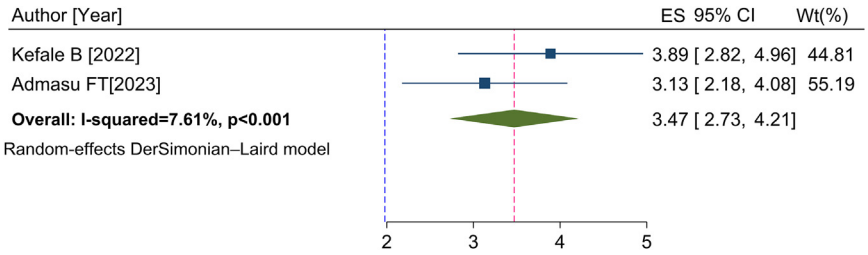

Figure 4. Forest plot showing the association of age- and cancer-related thrombosis

patients on the African continent was 11.65%. This estimated value is higher than the results of meta-analysis that was conducted by incorporating American, European, and Asian studies that showed that the pooled prevalence of thrombosis associated with cancer was 6%.[22] Evidence from various literatures has explained that cancer patients in developing countries are at high risk of developing thrombosis, as patients with cancer in Africa could have limited access to health care, including early diagnosis and treatment of cancer, which can lead to an increased risk of thrombosis.[62] In addition, a lack of awareness in relation to the risks and inadequate access to prophylactic anticoagulant drug therapy can further increase the risk of thrombosis among cancer patients.[63]

The result of this review also indicates that advanced-age patients living with cancer have a nearly 4-fold (OR = 3.47, 95% CI = 2.73–4.21) increased risk of developing thrombosis as compared to their younger counterparts. Evidence from previous studies similarly explains that the risk of cancer-related thrombosis is increasing significantly with age.[64] This could be because the body's natural anticoagulant production, such as protein C and protein S, has potentially decreased in cancer patients in advanced age, which can lead to a reduced ability to prevent blood clotting.[65] In addition, older cancer patients could have limited physical activities and underlying chronic diseases, which increase the risk of thrombosis.[66]

This review found that the likelihood of developing thrombosis among cancer patients with each additional chronic comorbid disease was five times higher than that of individual cancer patients without additional disease.[67] Comorbidities that occur alongside cancer can significantly increase the risk of developing thrombosis (blood clots). This might be due to various comorbidities associated with chronic inflammation and affect fibrin clot, which can lead to a hypercoagulable state and increases the risk of developing thrombosis.[68] Hormonal imbalances associated with certain disease conditions can also increase the risk of thrombosis.[69] The prevention, early identification, and management of comorbidities can help reduce the risk of thrombotic complications in patients with cancer.

Our findings also revealed that increased levels of D-dimer were independent predictors of an increased risk of developing thrombotic events among cancer survivors. Several studies that support our findings have reported the association between high levels of D-dimer and cancer-related thrombosis.[70,71] This might be due to the fact that tumor-induced hypercoagulability, systemic inflammatory response, and certain cancer treatments can work on the activation of the coagulation cascade, which in turn increases the magnitude of the plasma level of the biomarker D-dimer.[72] Monitoring D-dimer levels may help identify patients at high risk of developing VTE and inform therapeutic strategies to prevent or treat this complication.

Conclusion, implication, and recommendation

Our study identified that cancer-related thrombosis have been a significant public health burden in Africa as compared with other continents. The results of this review indicate that the overall magnitude of cancer-related thrombosis was 11.65%. This means at least 3 out of 25 cancer patients are at increased risk of developing thrombosis. The findings of this research also demonstrated the potential impact of various factors such as advanced age, comorbid disease, and increased level of D-dimer on cancer-related thrombosis.

Moreover, our work has not only addressed the existing gaps in the literature but has also presented practical implications for stakeholders. The insights provided can assist policymakers, practitioners, and decision-makers in making informed choices, implementing effective strategies, and maintaining better outcomes in thromboembolism events in cancer. Identifying and understanding the magnitude of CAT can have significant implications for patients, healthcare providers, and the overall healthcare system.

Based on the finding, it is better to provide training and capacity-building programs for healthcare providers in Africa on the prevention, diagnosis, and management of cancer-related

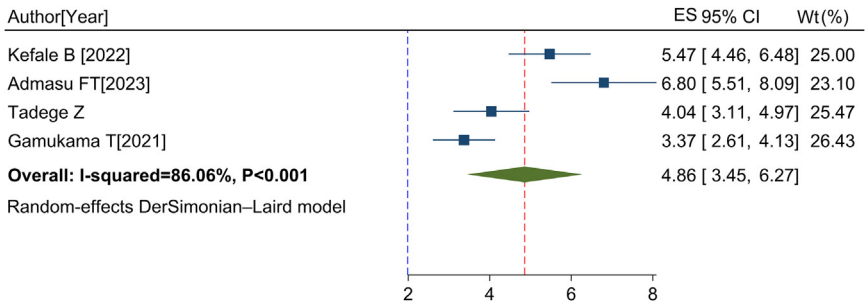

Figure 5. Forest plot showing the association of comorbid conditions and cancer-related thrombosis

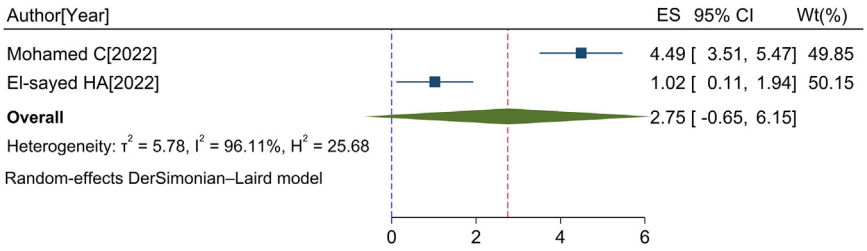

Figure 6. Forest plot showing the association of level of D-dimer and cancer-related thrombosis

thrombosis. Make international collaboration and research partnerships to develop innovative solutions for cancer-related thrombosis in Africa. It also needed to develop standardized evidence-based multidisciplinary approach care guidelines, implement thrombosis screening programs for cancer patients in Africa, and focus on comprehensive treatment including anticoagulants.

Limitations of the study

Despite our efforts to analyze and characterize CAT through various parameters such as geographical regions, country-level data, and specific cancer phenotypes, we face a notable limitation in our ability to accurately describe this phenomenon concerning cancer stages and different treatment statuses. This limitation arises primarily because the articles included in our study did not focus on these critical aspects.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Mr. Astewle Andargie Baye (astewlea@gmail.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data relevant to this study have been included in the manuscript/supplementary material.
- The code/datasets supporting the current study have not been deposited in a public repository but are available from the lead contact on request.
- All the original contributions presented in the study are included in the article/supplementary material**.** Further inquiries can be directed to the lead contact.

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AUTHOR CONTRIBUTIONS

A.A.B., writing—original draft, writing—review & editing, data curation, methodology, supervision, conceptualization, formal analysis, project administration, validation, investigation, resources, visualization, and software; A.T., writing—original draft, writing—review & editing, data curation, methodology, supervision, conceptualization, formal analysis, project administration, validation, investigation, resources, visualization, and software; Y.T., writing—review & editing, data curation, methodology, project administration, validation, investigation, resources, visualization, and software; B.Y., writing—review & editing, data curation, methodology, supervision, formal analysis, project administration, validation, investigation, resources, and visualization; D.K., writing—original draft, writing—review & editing, data curation, methodology, supervision, formal analysis, project administration, validation, investigation, resources, and visualization; L.Y., writing—review & editing, data curation, methodology, supervision, formal analysis, project administration, validation, investigation, resources, and visualization; B.M., writing—original draft, writing—review & editing, data curation, methodology, supervision, formal analysis, project administration, validation, investigation, resources, and visualization; B.B., writing—original draft, writing—review & editing, data curation, methodology, supervision, formal analysis, project administration, validation, investigation, resources, and visualization; A.T.D., writing—original draft, writing—review & editing, data curation, methodology, supervision, formal analysis, project administration, validation, investigation, resources, and visualization; D.H., writing–original draft, writing—review & editing, data curation, methodology, supervision, conceptualization, formal analysis, project administration, validation, investigation, resources, visualization, and software.

DECLARATION OF INTERESTS

The authors declare no competing interests. All authors assure that there are no financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS
  - Experimental model
  - Ethics approval and consent to participate
- METHOD DETAILS
  - Information sources and search strategies
  - Inclusion and exclusion criteria
  - Outcome measurement
  - Study screening
  - Quality appraisal
  - Data extraction
- QUANTIFICATION AND STATISTICAL ANALYSIS

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Microsoft Excel 2010	Microsoft office	https://microsoft-excel-2010.en.download.it/
Endnote X5	Thomson Scientific	https://endnote.com/downloads
Stata 17	Stata Corp LLC	https://www.stata.com/
International prospective register of systematic reviews & meta-analysis	Prospero	https://www.crd.york.ac.uk/prospero/ (Unique ID: CRD42024572725)

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Experimental model

As this study is a systematic review and meta-analysis, it utilizes existing literature rather than employing the experimental models prevalent in the life sciences.

Ethics approval and consent to participate

Ethical approval was not sought for this study because the study does not contain any animal or direct human participants for experiments.

METHOD DETAILS

Information sources and search strategies

This systematic review and meta-analysis focused on the magnitude of cancer related thrombosis in Africa. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed to report our results. Articles done from 2009 to 2024 were included in the search and eligible articles were downloaded into reference manager software. To obtain key literature, comprehensive search was conducted in the following databases: PubMed, EMBASE, CINAHL, Scopus and Epistemonikos. WHO Institutional Repository for Information Sharing (IRIS) and African Journals Online databases were also used. The search results were minimized by selecting studies published in English and conducted on humans. In addition, the researchers found related articles through a desk review of the gray literature available on local shelves and from reviewing the reference lists of already identified journal articles. Additional search engines such as Google and Google Scholar were used to incorporate additional search study results not in electronic databases. Unpublished theses and dissertations are also investigated at institutional repository centers. Finally, the reference lists of included studies were screened for additional articles. The search of electronic engines and databases was performed with proper Medical Subject Headings (MESH), and for every topic, the terms were combined with the appropriate Boolean operator ‘‘OR’’, and the concepts were combined with the Boolean ‘‘AND’’. Two independent researchers systematically conducted it. The search from the above-mentioned databases was done using the following key terms: "(Epidemiology)" OR "(prevalence)" OR "(magnitude)" OR "(incidence)" AND (cancer) OR (tumor) OR (neoplasms) AND (related) OR (associated) AND (superficial) OR (deep) AND arterial OR venous AND ("thrombosis) ‘‘OR "(thromboembolism) ‘‘AND ("Africa") OR "(African countries) OR (African nations: This is performed by entering each countries in Africa) (DATA S2). This study is registered in the PROSPERO platform with the registration (ID: CRD42024572725).

Inclusion and exclusion criteria

The study inclusion criteria was assessed and done by the primary author (AA), (DH) and (AT) using a two-stage approach. Initially, studies were screened based on all English-language titles and abstracts. At this stage, all studies reporting the prevalence of thromboembolism events among cancer patients in Africa were considered. Then, based on the predetermined inclusion criteria, a full-text assessment was performed. Only those studies conducted using internationally accepted diagnostic, laboratory and screening equipment to diagnose and for screen cancer related thrombosis without considering their age, cancer stage, type, primary site and treatment status were included.

Animal studies, systematic and Meta-analysis, and studies not reporting the outcome of interest quantitatively (narrative studies) were excluded from this systematic review and meta-analysis. Published articles other than English language and results focusing on non-cancer associated thrombosis were also excluded.

Outcome measurement

The primary outcome interest of this review was to identify cancer associated thrombosis. Cancer associated thrombosis is clinically diagnosed and identified as venous thromboembolism, which comprises deep vein thrombosis and/or pulmonary embolism in patients with cancer. It is the formation of a blood clot inside a blood vessel that is associated with cancer. All the studies that were part of this review and analysis fulfilled the following PICOS/PECOS format requirements:

Population/participant: All individuals diagnosed and confirmed as cancer patients.
Intervention/Exposure: Any associated factor that impacts thrombosis in cancer patients.
Comparator: Individuals without cancer.
Outcome: Magnitude of cancer related thrombosis in Africa.
Study type: Observational studies reporting magnitude of cancer related thrombosis.

Study screening

The potential relevance of the various databases, registers, and other source search results was examined independently by the three researchers (AA, AT & DK). It was conducted in a two-step distinct process. The first step was to remove duplicates. To do this, certain criteria were used. As a result, data and reference management software such as Endnote-version X5 was used to collect and organize the literature search outcomes. Duplicates and irrelevant search results were removed with regard to location of the studies, and outcome of interest. The second step was sorting of the studies based on titles. The researchers carefully read the titles and the irrelevant were excluded. Abstracts of relevant studies were examined based on the predetermined inclusion and exclusion criteria of the literature. It was conducted without considering age, gender, income level of the nation, specific cancer site and stage. The screening results for eligible studies of two groups of authors were compared. The discrepancy was resolved by the third author through discussion. Furthermore, the eligibility of the studies to be included for final data extraction was reassessed using a quality appraisal checklist. The selection process and the valid reason for exclusion have been documented based on the modified PRISMA guideline flow diagram (Data S3).

Quality appraisal

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA) guide-lines.

The modified version of the Newcastle-Ottawa scale (NOS), a critical appraisal tool, was used to evaluate the methodological quality and the reliability of individual studies. Potential sources of bias or systematic errors in the design, methods, or analysis of each study were identified. And the final decision for data extraction was based on this risk of bias assessment results. Newcastle Ottawa scale is a validated critical appraisal tool based on a star rating system, with each study receiving a maximum of ten for cross-sectional and case-control and 9 for cohort studies. Selection, comparability, and outcome/exposure are the three components and parameters of the tool. Finally, the quality score of each study was calculated as the sum of the scores. Articles with NOS quality assessment score of six or higher were regarded as being of excellent quality and eligible for the final inclusion and data extraction.[73] Three authors separately checked the quality of each study, and any potential disagreements were resolved through discussion (Data S4).

Data extraction

After assessing the methodological quality of each study, all the relevant information was extracted by two authors independently using a standardized data abstraction format designed by Microsoft Excel. The key variables such as first author name, study setting, year of study, year of publication, magnitude of the outcome, the sample size, and prevalence of an outcome (cancer related thrombosis) were the basis for the data extraction.

QUANTIFICATION AND STATISTICAL ANALYSIS

The extracted data was modeled onto stata software version 17 (Stata Corp LLC, College Station, Texas 77845 USA). As the objective of the review was to determine the pooled magnitude of cancer related thrombosis, a random-effects model, the DerSimonian–Laird method of meta-analysis, was used. To present the overall magnitude of the outcome, forest plots were generated. Statistically, the existence of heterogeneity across the studies was identified using Higgins I^2 statistics. If the estimated value of I^2 is <30%, 30–60%, 50–90, 75–100%, it is interpreted as low, moderate, substantial, and considerable level of heterogeneity among the studies respectively.[74] To deal with the existing heterogeneity, first the data were cross-checked for mistakes, then subgroup analysis, and sensitivity analysis to identify a single study effect was performed. Meta regression analysis was also done to explore the source of heterogeneity using sample size and regions as covariates. Qualitative and quantitative analysis was used to determine publication bias. Qualitatively, visual inspection of the symmetric distribution of individual studies in the funnel plot was used. And the trim and fill analysis was also considered. Egger's regression test was done quantitatively to identify small study effects. Statistically, a non-significant value (P-value >0.05) of the test was considered to minimize evidence of publication bias. The overall meta-estimate of thrombosis has presented with percent. Odds ratio (OR) was used to identify association between dependent and independent variables.