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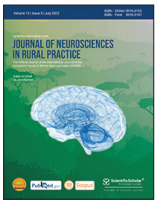

*Systematic Review*

# Systematic review and meta-analysis of studies comparing baseline D-dimer level in stroke patients with or without cancer: Strength of current evidence

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## ABSTRACT

**Objectives:** D-dimer levels are increased in stroke and cancer. Cancer patients are at a higher risk of stroke. However, the evidence is unclear if high D-dimer in stroke patients can suggest the diagnosis of concomitant cancer or the development of stroke in a cancer patient. The objective is to assess the evidence available on the baseline D-dimer level in stroke patients with and without cancer.

**Materials and Methods:** We conducted the systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. We searched PUBMED, Cochrane, ScienceDirect, and Scopus for potentially eligible articles published till June 2023. All the review steps were iterative and done independently by two reviewers. The Newcastle-Ottawa scale tool was used to assess the quality of included studies for case control and cohort studies and the Agency for Healthcare Research and Quality tool for cross-sectional studies. The qualitative synthesis is presented narratively, and quantitative synthesis is shown in the forest plot using the random effects model. $I^2$ of more than 60% was considered as high heterogeneity.

**Results:** The searches from all the databases yielded 495 articles. After the study selection process, six papers were found eligible for inclusion in the qualitative and quantitative synthesis. In the present systematic review, 2651 patients with ischemic infarcts are included of which 404 (13.97%) patients had active cancer while 2247 (86.02%) did not. The studies included were of high quality and low risk of bias. There were significantly higher baseline D-dimer levels in stroke patients with cancer than in non-cancer patients with a mean difference of 4.84 (3.07–6.60) $P < 0.00001$.

**Conclusion:** D-dimer is a simple and relatively non-expensive biomarker that is increased to significant levels in stroke patients, who have cancer and therefore may be a tool to predict through screening for active or occult cancer in stroke patients.

**Keywords:** Cancer, D-dimer, Stroke, Prognosis, Cerebral infarction

## INTRODUCTION

The D-dimer is the fibrin degradation product at minimally detectable levels in normal individuals; however, it increases in stroke patients, thrombolytic/fibrinolytic disorders, and critically sick patients.[1-3] Patients with malignancy are especially prone to develop ischemic stroke by various mechanisms including hypercoagulable state and tumor occlusion.[3-8] Various studies have reported that high plasma D-dimer levels can be seen in cancer-associated ischemic stroke patients, further supporting the assumption that hypercoagulability is a significant risk factor for developing stroke in cancer patients.[2,3,9-13] Studies have shown that abnormal D-dimer levels and multiple territories of infarcts are predictors of malignancy in a stroke patient.[2,14] In a study, the authors investigated the relationship between D-dimer levels in cancer-associated stroke patients after stroke treatment. They suggested that higher D-dimer levels were associated with poor short-term outcomes.[15] Higher levels of D-dimer have been found in the cerebral infarct in cancer patients than in non-cancer patients in several studies. In addition, studies have found that D-dimer might be an important marker in the screening

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of stroke in malignancy patients and in differentiating between cryptogenic stroke and stroke with determined etiology in patients with cancer.[4,16,17] A systematic review found that the D-dimer levels were elevated in the stroke and are a non-expensive marker; however, it is not specific or sensitive to the type of stroke and cannot replace the traditional clinical and radiological methods for stroke diagnosis.[18] The conflicting findings from the studies necessitate conducting a systematic review to establish the evidence on the baseline D-dimer levels in infarct in cancer versus non-cancer patients. In this systematic review and meta-analysis, we aimed to assess the evidence regarding the hypothesis that the baseline D-dimer levels are higher in patients, who present with ischemic stroke and who had a cancer diagnosis than in patients, who do not have a cancer diagnosis at the time of clinical presentation.

## MATERIALS AND METHODS

The present systematic review and meta-analyses followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and the meta-analyses and the Cochrane Manual of Systematic Reviews and Meta-analysis.[19] Two reviewers independently performed all the review process steps, and the third reviewer was consulted in case of any discrepancy.

### Search

We searched the databases including PubMed, Scopus, Central Cochrane Registry of Controlled Trials (The Cochrane Library), and ScienceDirect until June 2023. In addition, the reference list of included studies and other relevant data in addition to potentially eligible studies were searched; the details of search terms are listed in Table 1. The search strategy was prepared and pilot-tested to maximize the specificity and sensitivity of the search terms.

**Table 1:** Details of databases and search terms.

| Database | Search terms |
|---|---|
| PubMed | ((“stroke”[MeSH Terms] OR “stroke”[All Fields] OR “strokes”[All Fields] OR “stroke s”[All Fields]) AND (“fibrin fragment d”[Supplementary Concept] OR “fibrin fragment d”[All Fields] OR “d dimer”[All Fields]) AND (“cancer s”[All Fields] OR “cancerated”[All Fields] OR “canceration”[All Fields] OR “cancerization”[All Fields] OR “cancerized”[All Fields] OR “cancerous”[All Fields] OR “neoplasms”[MeSH Terms] OR “neoplasms”[All Fields] OR “cancer”[All Fields] OR “cancers”[All Fields])) AND (1000/1/1:2023/6/6[pdat]) |
| Cochrane | 12 Trials matching stroke D-dimer cancer in title abstract keyword |
| Scopus | Title, abstract, keywords: Stroke D-dimer cancer |
| ScienceDirect | Title, abstract, keywords: Stroke D-dimer cancer |

### Inclusion/exclusion criteria

Studies reporting on D-dimer levels in infarct patients in cancer and non-cancer were included in the study. The criteria for inclusion were original articles written in English, and the date of publication was between the date of inception and June 6, 2023. The submissions excluded were review articles, brief reports, letters, conference abstracts, and papers not written in English. Studies that did not have a non-cancer group as a comparison were excluded from the study.

### Study selection and data extraction

Two reviewers did an independent screening of studies retrieved from the search sources regarding eligibility based on title and abstracts. Then, the full-length articles were retrieved. A third review author was consulted for a decision in case of any discrepancy. The data extraction was done in a pre-designed proforma. Data collected included study authors, year, country of origin, sample size, gender, age, and D-dimer values according to the groups (cancer vs. non-cancer).

### Evaluation of the quality of the studies

The quality of the case–control and cohort studies was assessed using the Newcastle-Ottawa scale (NOS). The NOS mainly consists of three domains of selection, comparability, and outcome and has a subset of questions in each domain.[20] The quality of included studies was through the Newcastle-Ottawa Quality Assessment Scale, and studies with scores of 7 were considered of high methodological quality. Those with scores of 4–5 were considered moderate quality. The study quality of the cross-sectional study was done using the Agency for Healthcare Research and Quality (AHRQ), an 11-question scoring system with one score for each item.[21] A score of 0–4 indicates a high risk of bias, 5–7 means a moderate risk, and 8–11 shows a low risk of bias.[21]

### Statistical analysis

The random effects analysis model was calculated using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). We analyzed the mean difference for each outcome using the generic method of the inverse of the variance to combine this data. We expected different units and effect estimates of reporting D-dimer levels in individual studies; and therefore, in studies where mean values were not reported, we calculated the mean values from reported effect estimates and then used mean difference as effect estimate for meta-analysis to avoid the potential problems of using standardized mean difference in such a situation.

[22] The originally reported values in individual studies and converted values used for quantitative synthesis along with the references are detailed in supplementary Table S1. In the studies where units of D-dimer were not reported, we assumed the most commonly used unit of D-dimer for conversion and used in quantitative analysis and performed sensitivity analysis. Heterogeneity was assessed by calculating Chi-square ($I^2$), with the high heterogeneity of the studies included in the analysis being above 60%.

## RESULTS

### Study selection

The database search retrieved 495 articles; after removing duplicates (160), 335 records were screened for eligibility, and 297 articles were excluded. The full text of the 39 articles was evaluated; 33 articles were excluded [Table 1][10,13,15,17,23-51] with reasons, and six articles [Table 2][16,52-56] were included in systematic review and meta-analyses [Figure 1]. Characteristics of the studies included are shown in Table 2. Figure 1 shows the study flow diagram of study search, screening, text retrieval, and inclusion in the qualitative and quantitative synthesis.

### Quality assessment and risk of bias

The quality of the included studies, as assessed by the NOS for cohort and case–control studies, is shown in Table 3. The median quality was 7/9. Most of the included studies meet the majority criteria in the quality assessment tool. The study of Beyeler *et al.*[52] scored 9/11 in the AHRQ tool suggesting a low risk of bias in the study.

### Characteristics of included studies

Three studies were from China[16,55,56] and one each from Switzerland, Japan, and Turkey.[52-54] All the included

**Table 2:** Excluded studies with reasons.

| Study (Year) | Reason |
|---|---|
| Alvarez-Perez *et al.*, 2012[51] | No non-active cancer group |
| Amiri-Nikpour and Husseinzadeh, 2016[23] | Full text not available |
| Bang *et al.*, 2023[24] | No separate group to answer research question |
| Bonnerot *et al.*, 2016[25] | No non-active cancer group |
| Cen *et al.*, 2023[26] | No non-active cancer group |
| Di Castelnuovo *et al.*, 2014[27] | Patients with coronary artery disease did not answer |
| Ellis *et al.*, 2018[28] | Study does not separately provide D-dimer data in cancer patients |
| Markus, 2020[29] | Editorial |
| Ito *et al.*, 2018[30] | No non-active cancer group |
| Kim *et al.*, 2021[17] | No well-defined cancer and non-cancer groups |
| Kono *et al.*, 2012[10] | Detailed FDP values not available separate for cancer and non-cancer groups |
| Liu *et al.*, 2021[31] | Study does not separately provide D-dimer data in cancer patients |
| Nahab *et al.*, 2020[32] | Study does not separately provide D-dimer data in cancer patients |
| Nakajima *et al.*, 2022[15] | No non-active cancer group |
| Nam *et al.*, 2017[33] | No non-active cancer group |
| Nam *et al.*, 2023[34] | No non-active cancer group |
| Nezu *et al.*, 2018[35] | No non-active cancer group |
| Nickel *et al.*, 2021[36] | Mix of population, no separate cancer group |
| Ohara *et al.*, 2020[13] | Review article |
| Pan *et al.*, 2021[38] | Study does not separately provide D-dimer data in cancer patients |
| Pan *et al.*, 2022[37] | No non-active cancer group |
| Pieper *et al.*, 2000[39] | Mix of population |
| Rodrigues *et al.*, 2014[40] | Conference abstract |
| Rosenberg *et al.*, 2020[41] | Study does not separately provide D-dimer data in cancer patients |
| Ryu *et al.*, 2017[42] | No non-active cancer group |
| Schultz *et al.*, 2022[43] | Conference abstract |
| Shen *et al.*, 2020[44] | Study does not separately provide D-dimer data in cancer patients |
| Tardy *et al.*, 1998[45] | Study does not separately provide D-dimer data in cancer patients |
| Tsushima *et al.*, 2020[46] | No non-active cancer group |
| Wang *et al.*, 2022[47] | No non-active cancer group |
| Wei *et al.*, 2020[48] | No non-active cancer group |
| Yamaguchi *et al.*, 2019[49] | No non-active cancer group |
| Zhang *et al.*, 2019[50] | Systematic review and meta-analyses |

FDP: Fibrinogen degradation products

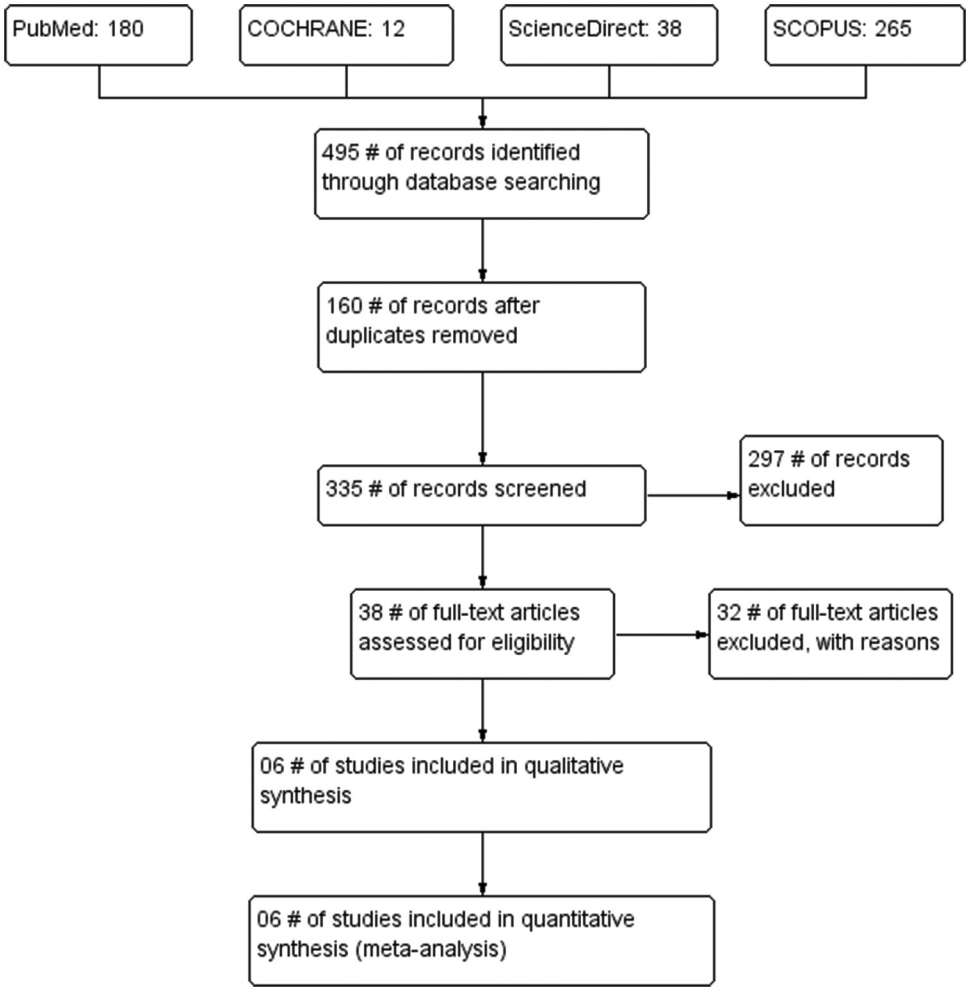


**Figure 1:** Preferred reporting items for systematic reviews and meta-analysis study flow diagram, #: Number.

studies were retrospective. In the present systematic review, 2651 patients with ischemic infarcts are included of which 404 (13.97%) patients had active cancer while 2247 (86.02%) did not. In four studies,[16,52-54] infarct patients without active cancer were proportionately more than cancer patients. At the same time, the two studies[55,56] had almost equal proportions of infarct patients in the cancer and non-cancer groups. The mean age of the patients included in all the studies was more than 60 years with similar gender distribution. The characteristics of the included studies are shown in Table 4.

### Results of individual studies

Guo *et al*.[16] reported their results from 528 patients in a retrospective cohort study of which 98 had cancer while 430 did not have active cancer. The authors defined active cancer as the occurrence of cancer or recurrence within one year of the stroke diagnosis or cancer diagnosed before the stroke but with incomplete treatment. The plasma D-dimer levels in the cancer patients were much higher than in the non-cancer patients (7.59 ± 10.96 vs. 0.66 ± 1.83). The authors found significantly higher D-dimer levels in stroke patients with active cancer than in no cancer; however, there was no significant difference between the no-cancer group and inactive cancer group, i.e., the patients who had cancer before stroke but received treatment and were in complete remission. This suggests that active cancer affects the coagulation cascade, and remission from cancer results in the resolution of the coagulation abnormality. Further, the authors found that multiple infarct territories in stroke are seen more in cancer patients than in non-cancer patients. The most common malignancies resulting in stroke were gastrointestinal followed by lung and hematological malignancies. In the study, more than 60% of stroke patients with cancer had D-dimer levels above 1.55 mg/L while only 7.9% non-cancer group had D-dimer levels above this cutoff. This cutoff value had a sensitivity of 59.2% and a specificity of 91.8%. The authors further concluded that the abnormal D-dimer value was insufficient to suggest the presence of concomitant cancer. If the D-dimer values were as high as

**Table 3:** Quality of studies assessment by Newcastle-Ottawa scale tool.

| S. No. | Groups | Selection | | | | Comparability | Outcome | | | Total score |
|---|---|---|---|---|---|---|---|---|---|---|
| | Study Id | Representativeness of sample | Selection of the non-exposed cohort | Ascertainment of Prognostic variable | Demonstration That Outcome of Interest Was Not Present at Start of Study | Comparability of cohorts based on the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | |
| 1. | Guo *et al.*, 2014[16] | ★ | ★ | ★ | ★ | ★ | ★ | ★ | ★ | 8/9 |
| 2. | Gon *et al.*, 2017[53] | ★ | ★ | ★ | ★ | ★ | ★ | ★ | | 7/9 |
| 3. | Sorgun *et al.*, 2018[54] | ★ | ★ | ★ | ★ | ★ | ★ | ★ | | 7/9 |
| **Case Control study** | **Study Id** | **Case definition adequate?** | **Representativeness of the cases** | **Selection of controls** | **Definition of controls** | **Comparability of cases and controls based on the design or analysis** | **Ascertainment of exposure** | **Same method of ascertainment for cases and controls** | **Non-response rate** | |
| 1. | Wang *et al.*, 2018[56] | ★ | ★ | ★ | ★ | ★ | ★ | ★ | | 7/9 |
| 2. | Wang *et al.*, 2019[55] | ★ | ★ | ★ | ★ | ★ | ★ | ★ | | 7/9 |

★Indicates that it meets criteria in Newcastle-Ottawa Scale

**Table 4:** Characteristics of included studies.

| Study (Author) | Country | Study type | Sample size | | Age (Years) | | Gender (Male/Female) | | D-dimer | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cancer | No active cancer | Cancer | No active cancer | Cancer | No active cancer | Cancer | No active cancer |
| Beyeler *et al.*, 2022[52] | Switzerland | Single-center retrospective, cross sectional | 61 | 940 | Age at admission (median, IQR) 76.8 (71.183.4) | 73.5 (62.582.3) | Female 24/61 | Female 390/940 | D-dimer in µg /L (median, IQR) 1689 (652–6852) | 701 (367.5–1524.5) |
| Gon *et al.*, 2017[53] | Japan | Retrospective cohort | 12 | 108 | 64 (54–75) | 65 (51–74) | Female=8 | Female=43 | D-dimer (µg /mL) 6.2 (1.2–12.0) | 0.5 (0.3–0.9) |
| Guo *et al.*, 2014[16] | China | Retrospective cohort | 98 | 430 | 70.95 ± 13.61 | 69.0 ± 12.6 | Male% 59.3 | 69.1 | D-dimer (mg/L) 7.59±10.96 | 0.66±1.83 |
| Sorgun *et al.*, 2018[54] | Turkey | Retrospective cohort | 46 | 573 | Age, year, Mean±SD 70.70±11.04 | 69.30±13.52 | Female=17 Male=29 | Female=273 Male=300 | D-dimer, Median (Min–Max) 1,519.0 (362.0–12,487.0) | 590.5 (42.0–3,191.0) |
| Wang *et al.*, 2019[55] | China | Retrospective case–control study | 126 | 120 | Age, years, M (IQR) 63 (41–88) | 73 (51–85 | Male% 80 (63.5) | 78 (65.0) | D-D, mg/L 5.7 (4.1–11.7) | 1.2 (0.7–6.8) |
| Wang *et al.*, 2018[56] | China | Retrospective case control | 61 | 76 | 64.7±11.8 | 65.4±12.6 | Male% 43 (56.6) | 32 (52.5) | D-dimer (µg/mL) 0.84±0.80 | 10.81±13.19 |

SD: Standard deviation, IQR: Interquartile range

5.5 mg/L, there should be a comprehensive search for cancer, as the specificity and positive predictive values were >93%.

Gon *et al.*[53] conducted a retrospective analysis of the ability of D-dimer values to predict occult cancer in 120 cryptogenic stroke patients without cancer at diagnosis. The authors defined cryptogenic stroke as a stroke without a defined identified etiology despite extensive evaluation. Of these, 12 patients (10%) had occult cancer. Among 12 patients with occult cancer, six (50%) had adenocarcinoma, five had an extensive disease in metastasis, and nine (75%) patients had ischemic lesions in multiple vascular territories. The D-dimer levels were much higher in the occult cancer group than in the non-cancer group (median 6.2 vs. median 0.5).

Sorgun *et al.*[54] reported the predictive value of D-dimer in a retrospective analysis of 619 stroke patients of which 46 had cancer and 573 had no active cancer. The authors defined active cancer as active cancer before stroke diagnosis. The study's common causes of cancer leading to stroke were bladder cancer followed by gastric, lung, and hematological malignancies. The D-dimer levels were significantly higher in the cancer group than in the non-cancer group (1,519.0 vs. 590.5). The authors did not report the unit of D-dimer in their study.

Wang *et al.*[56] study included 137 acute ischemic stroke patients, 61 with cancer and 76 without cancer, reported higher D-dimer values in the cancer group. The most common cancers in the acute ischemic group were gastric, lung, and colorectal. In 14 patients (23.0%), cancer was detected later to the ischemic stroke with a thorough examination after admission suggesting that such stroke patients with higher D-dimer values should be screened for the presence of cancers. The cutoff value of 2.785 μg/mL of D-dimer for differentiating stroke with cancer from stroke without cancer has a sensitivity of 50.9% and specificity of 98.5%. Furthermore, patients with D-dimer higher than the cutoff values in the cancer group were more likely to have multiple territories of ischemic lesions.

Wang *et al.*[55] in their retrospective case–control study included 246 stroke patients (126 with cancer and 120 as control). The patients included were adults, and active cancer was defined as a new cancer diagnosis, metastasis, recurrence or ongoing cancer treatment within one year before the stroke diagnosis. The patients with confounders such as other central nervous system (CNS) diseases and cardiac, hepatic, and renal diseases were excluded. The authors found that the median levels of D-dimer were higher in the cancer group than in the control group (5.7 mg/L vs. 1.2 mg/L).

Beyeler *et al.*[52] in their single-center retrospective cross-sectional study included 1001 stroke patients (61 with cancer and 940 without cancer). The authors defined active cancer as a new cancer diagnosis, recurrent cancer or metastasis within six months before the stroke diagnosis and occult cancer as a cancer diagnosis within one year after the stroke diagnosis. Among the 61 patients with active malignancy at the stroke diagnosis, 22 had occult and 39 had known cancer. The median D-dimer was higher in the cancer group than in the non-cancer group (1689 μg/L vs. 701 μg/L).

### Synthesis of results

The meta-analysis of the included studies using the random effects model showed that the D-dimer values were significantly higher in stroke patients with cancer than without cancer with a mean difference of 4.84 (3.07–6.60) $P < 0.00001$. There was a high heterogeneity of 85%. The high heterogeneity is likely due to clinical heterogeneity because of diverse populations, inclusion, exclusion criteria, confounders, and biases in the included studies. The forest plot analysis of the included studies is shown in Figure 2a. Figure 2b shows that the results of the sensitivity analysis with the study by Sorgun *et al.*[54] were removed, as we assumed the most common unit of D-dimer and the unit was not reported in the study; we found that the mean difference increased to 5.53 and 95% confidence interval (CI) of 3.10–7.97. Figure 2c shows that the results of the study by Beyeler *et al.* were removed from the analysis, as the data presented in the study were not following the normal distribution. Figure 2d shows that the results of both the studies by Sorgun *et al.* and Beyeler *et al.* were removed from the analysis, and there was further increase in the net effect estimate to mean difference of 6.58 with 95% CI of 4.00–9.16.

## DISCUSSION

Stroke is the second leading cause of CNS involvement in cancer patients after metastatic involvement. Cancer patients are prone to stroke, and stroke in cancer happens due to altered homeostasis and activation of coagulation cascade either due to intracranial metastasis or coagulation disorder or vascular injury secondary to the chemotherapy, radiotherapy or tumor embolization.[2,57-59] Additional causes of stroke in cancer include non-bacterial thrombotic endocarditis, diffuse thrombosis of cerebral vessels or septic fungal emboli, which occur in leukemic patients, who underwent bone marrow transplantation.[2,57,58]

In the present systematic review, we have searched multiple databases and identified five retrospective cohort studies and one cross-sectional study. The pooled estimate from the included studies suggests that the D-dimer values are significantly higher in stroke patients, who had cancer than those without cancer. Although there was high heterogeneity as seen from the forest plot, the effect estimates of all the individual studies show the same direction of effect; therefore, the confidence in the results is increased. Further, some individual studies have shown that D-dimer levels

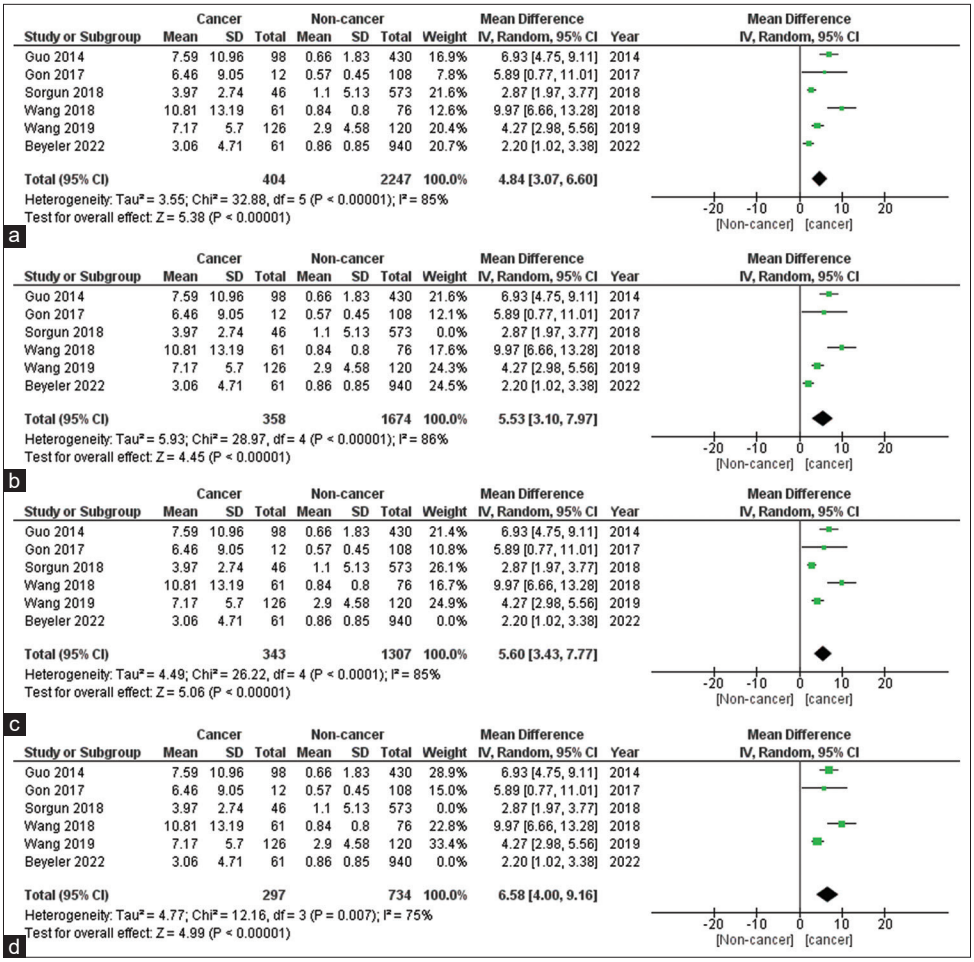


**Figure 2:** (a) Forest plot diagram of D-dimer values in cancer and non-cancer group; (b) forest plot diagram of sensitivity analysis by removing study by Sorgun *et al.*; (c) forest plot diagram of sensitivity analysis by removing study by Beyeler *et al.*; and (d) forest plot diagram of sensitivity analysis by removing study by Sorgun *et al.* and Beyeler *et al.* SD: Standard deviation, CI: Confidence interval.

above 5.5 should prompt a thorough screening of underlying cancer. The pooled effect estimate from our present review is like the cutoff values reported in other studies.

The differences in the studies could be due to the methodology with most studies being retrospective and the variation in the cancer studies. It has been found that bleeding was most likely in leukemia patients while infarction was the most common cerebrovascular finding in carcinoma patients.[60] In an autopsy study, only 7.4% had clinical symptoms while 14.6% had pathological evidence of cerebrovascular disease.[60]

In the study by Ryu *et al.*, the authors reported on the predictive value of D-dimer in predicting cerebral infarction in critically ill cancer patients (43 infarcts vs. 43 non-infarcts).[42] The study was retrospective and included only cancer patients. Patients were evaluated with diffusion-weighted magnetic resonance imaging based on clinical suspicion and found that there was no significant difference in the D-dimer among the patients with infarct or non-infarct, but D-dimer levels >8.89 μg/mL were more associated with the cryptogenic mechanisms of the stroke than the determined mechanisms of the stroke.[42]

## Strengths

A detailed and iterative process reduces the bias. We performed the sensitivity analysis by removing studies where conversion of data from the reported data could result in erroneous conclusions, and we found in the sensitivity analysis a net addition to the effect estimate of the mean difference. This adds strength and generalizability to the results of the analysis. Further, we have estimated the mean difference to avoid the potential problems of using standardized mean difference by converting the data reported in the individual studies to common units, mean,

and standard difference. This also adds to the generalizability and strength of the results obtained.

### Future implications and limitations

The stroke itself is associated with increased levels of D-dimer.[51,61] In the literature, it is published that the mortality from stroke in cancer patients is almost double that of stroke in cancer patients.[62-64] The present review is critical from a clinical viewpoint because it is helpful from the patient care perspective that cancer patients are prone to stroke, and many patients currently with stroke are harboring occult or active cancer and should be actively screened. Both these dimensions are essential to explore for better patient care and outcomes. Two different study designs are likely to provide answers to these questions. In our current review, all the included studies included patients with stroke and then looked at the presence or absence of cancer. The optimal methodology of meta-analysis of biomarker-based studies is still evolving. D-dimer is a very common thrombotic biomarker, which can be raised both in stroke and cancer. Therefore, the clinical significance of raised D-dimer in stroke patients with cancer may be a potential biomarker to differentiate cancer from non-cancer patients with stroke. Due to the heterogeneity of studies optimal threshold level of D-dimer (cut-off value) could not be ascertained in this study. As the included studies do not have a group of cancer patients without stroke for comparison, it cannot be stated conclusively whether the elevated D-dimer levels are because of the stroke or cancer. Further, the included studies have not performed the cancer screening comprehensively on all the patients, and this selection bias might influence the results obtained. The other scenario is where cancer patients are included, and then the comparison is drawn between the stroke and non-stroke groups. As both the disease processes are different but interact, several other parameters might affect the outcome of the interest being measured. Consequently, a more extensive study with multiple groups will be more helpful in addressing these questions.

## CONCLUSION

Baseline D-dimer levels are significantly higher in stroke patients with cancer than in non-cancer patients with stroke. There is a hypercoagulable state in cancer patients, and increased D-dimer levels contribute to an increased risk of stroke in cancer patients. D-dimer is a readily available, less expensive screening biomarker in stroke patients that may suggest screening for cancer. The strength of evidence is low due to fewer studies, and much larger prospective studies will provide a more substantial evidence based on baseline D-dimer in stroke patients with and without cancer.

### Ethical approval

Institutional Review Board approval is not required.

### Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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## SUPPLEMENTARY TABLE

**Supplementary Table S1:** The units and original data reported, conversion for quantitative synthesis and rational of conversion.

| Study (Author) | Sample size | | Unit | D-Dimer | | | | | | | Remarks for conversion calculations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cancer | | No active cancer | Cancer | | | No active cancer | | | | |
| Beyeler, 2022[52] | 61 | 940 | Reported: D-dimer in µg/L (median, IQR) | 1689 (652-6852) | 1689 | 652 | 6852 | 701 (367.5-1524.5) | 701 | 367.5 | 1524.5 | The values were converted from µg/L unit to mg/L and then the median values were converted to mean and standard deviation using the formula below. The text in the manuscript contains the values reported by authors, while the values in the forest plot are computed mean values for quantitative analysis. Reference: S.P. Hozo, B. Djulbegovic, and I. Hozo, *BMC Medical Research Methodology* 2005,5:13 |
| | | | Converted: D-dimer in mg/L (median, IQR) | | 1.689 | 0.652 | 6.85 | | 0.7 | 0.368 | 1.5245 | |
| | | | Converted: D-dimer (mg/L) (mean±standard deviation) | 3.06±4.71 | | | | 0.864±0.859 | | | | |
| Gon, 2017[53] | 12 | 108 | Reported: D-dimer (µg/mL) (median, IQR) | 6.2 (1.2–12.0) | 6.2 | 1.2 | 12 | 0.5 (0.3–0.9) | 0.5 | 0.3 | 0.9 | The values were converted from µg/mL unit to mg/L and then the median values were converted to mean and standard deviation using the formula below. The text in the manuscript contains the values reported by authors, while the values in the forest plot are computed mean values for quantitative analysis. Reference: S.P. Hozo, B. Djulbegovic, and I. Hozo, *BMC Medical Research Methodology* 2005,5:13 |
| | | | Converted: D-dimer (mg/L) (median, IQR) | | 6.2 | 1.2 | 12 | | 0.5 | 0.3 | 0.9 | |
| | | | Converted: D-dimer (mg/L) (mean±standard deviation) | 6.46±9.05 | | | | 0.57±0.45 | | | | |
| Guo, 2014[16] | 59 | 430 | Reported: D-dimer (mg/L) (mean±standard deviation) | 5.70±9.63 | 5.7 | 9.63 | | 0.66±1.83 | 0.66 | 1.83 | | The two means of the SRS group and the Hospital database group was combine using cochrane's formula. Reference: Altman DG, Machin D, Bryant TN and Gardner MJ. (2000) Statistics with Confidence Second Edition. BMJ Books ISBN 0 7279 1375 1. p. 28-31 Higgins JPT, Li T, Deeks JJ (editors). Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. |

*(Contd...)*

**Supplementary Table S1:** *(Continued).*

| Study (Author) | Sample size | | Unit | D-Dimer | | | | | | | Remarks for conversion calculations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cancer | | No active cancer | Cancer | | | No active cancer | | | | |
| Sorgun, 2018[54] | 46 | 573 | Reported: D-dimer, Median (Min-Max)<br>Converted: D-dimer (mg/L) (mean±standard deviation) | 1,519.0 (362.0-12,487.0)<br>2.74±3.03 | 1519 | 362.1 | 12487 | 590.5 (42.0-3,191.0) | 590.5 | 42 | 191 | Most common unit of D-dimer is assumed and median is converted to mean with standard deviaion |
| Wang, 2019[55] | 126 | 120 | Reported: D-dimer, mg/L (median, IQR) | 5.7 (4.1–11.7) | 5.7 | 4.1 | 11.7 | 1.2 (0.7–6.8) | 1.2 | 0.7 | 6.8 | The text in the manuscript contains the values reported by authors, while the values in the forest plot are computed mean values for quantitative analysis.<br>Reference:<br>S.P. Hozo, B. Djulbegovic, and I. Hozo, *BMC Medical Research Methodology* 2005,5:13 |
| | | | Converted: D-dimer (mg/L) (mean±standard deviation) | 7.17±5.7 | | | | 2.9±4.58 | | | | |
| Wang, 2018[56] | 61 | 76 | Reported: D-dimer (µg/ml) (mean±standard deviation) | 10.81±13.19 | 10.81 | 13.19 | | 0.84±0.80 | 0.84 | 0.8 | | The mean and SD for d-dimer calculated in mg/L units from µg/mL for the purpose of forest plot analysis. |
| | | | Converted: D-dimer (mg/L) (mean±standard deviation) | 10.81±13.19 | 10.81 | 13.19 | | 0.84±0.80 | 0.84 | 0.8 | | |

IQR: Interquartile range, SD: Standard deviation