REVIEW

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Is Sphingosine Kinase 1 Associated with Hematological Malignancy? A Systematic Review and Meta-Analysis

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Abstract

Background: Sphingosine kinase 1 (SphK1) is a lipid enzyme whose role in the etiology of cancer has been well explored. Here, a systematic review and meta-analysis were conducted to evaluate the association of SphK1 expression with hematological malignancy. **Materials and methods:** Relevant studies were identified through electronic databases (PubMed, Scopus, Embase, and OVID) and evaluated based on predefined inclusion and exclusion criteria. Quality assessment using the Newcastle-Ottawa Scale (NOS) was conducted, and pooled odds ratio (OR) was calculated to assess the association between SphK1 expression and hematological malignancy. **Results:** Nine studies meeting the inclusion criteria were included in the systematic review. These studies utilized various techniques to assess SphK1 expression in hematological malignancies. The quality assessment reported that the included studies were of moderate quality. Meta-analysis of eligible studies revealed a positive association between SphK1 expression and hematological malignancies at the protein level (OR = 52.37, 95% CI = 10.10 to 271.47, and P = 0.00001). The funnel plot indicated no publication bias among the included studies. However, the certainty of the evidence was low according to the GRADE assessment. **Conclusion:** Our study's findings support the link between SphK1 expression and hematological malignancies. SphK1 gene dysregulation may contribute to various malignancies, suggesting it could be a therapeutic target to improve patient outcomes. Further research is needed to understand SphK1's mechanistic role in hematological malignancies and its therapeutic potential.

Keywords: Sphingosine kinase- G-Protein Coupled Receptors- Blood Cancer- Biomarker- Odds ratio

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Introduction

In the last few decades, Sphingolipid metabolite has earned tremendous importance due to its pivotal role in cell fate determination in human health and disease [1-2]. The three key metabolites namely ceramide, sphingosine, and sphingosine 1 phosphate (S1P) play an important role in cell cycle and fate. Ceramide and sphingosine induce apoptosis, leading to cell cycle arrest and senescence, while S1P triggers pleiotropic signaling, leading to cell survival [2-6]. These sphingolipids with contradictory roles inside the cells create a balance between them termed "sphingolipid rheostat" and thus instruct the cell to either "stop" or "go" [2-3,7-8]. Sphingosine kinase (SphK), a rate-limiting enzyme that catalyzes the phosphorylation of sphingosine to form S1P is regarded as the key participant of this balance as it maintains the level of sphingolipids formation inside the cells. Thereby S1P accumulation causes cells to survive and decrease the formation of pro-apoptotic signaling lipid ceramide and sphingosine [7-9].

There are two isoforms of SphK: *SphK1* localized in the cytoplasm and translocates to the plasma membrane upon activation and SphK2 localized in the nucleus [2,4,10]. Many researchers have thoroughly examined *SphK1*'s role and identified it as a novel pharmacological therapeutic target to fight against various cancers including hematological malignancy [3,11-15]. While SphK2 regulates dual function by boosting the apoptotic lipid level inside the cells and suppressing cell growth [2-3,10]. Therefore, more investigations are required to ascertain SphK2's role. However, both SphK types generate S1P and it acts on one of the S1P-specific G-protein coupled receptors (GPCR) (S1PR1-S1PR5) for its autocrine and paracrine signaling [2-4]. Thus, S1P binding to GPCR exerts multiple biological effects such as cell growth, migration, proliferation, differentiation, inflammation, and angiogenesis which contribute to cancer pathogenesis

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[16-18].

Abundant studies have discussed *SphK1*'s oncogenic properties and correlated *SphK1* expression with poor prognosis [19-23]. Elevated *SphK1* expression marks an imperative function in metastasis, unstoppable cell proliferation, survival, and activation in numerous cancers including hematological malignancy [19, 21, 24-28]. Through S1P, *SphK1* activates many downstream signaling cascades such as Mcl-1, RTK, JAK/STAT, and PI3K/AKT pathways which then promote malignancy in blood [28-32]. Thus, activation of these signaling pathways leads to angiogenesis and cell survival by protecting cells from diverse cellular mechanisms like apoptosis and autophagy [25, 28, 30-31, 33]. Notably, many studies have also elucidated that over-expression of *SphK1* is responsible for drug resistance in patients [31, 34-35]. Due to its potent oncogenic characteristics, *SphK1* is considered a key target for improving hematological malignant patient survival.

Several case-control studies have been conducted addressing the association of *SphK1* with hematological malignancy. However, conducting a meta-analysis allows for a comprehensive synthesis of existing data, potentially offering more robust conclusions and insights. Furthermore, because most studies have small sample sizes and lack representativeness, a meta-analysis can address this issue by pooling data from multiple studies. As far as we are aware, no systematic review or meta-analysis has been conducted to assess the association between *SphK1* and hematological malignancy. Thus, a systematic review and meta-analysis were undertaken in light of the aforementioned oncogenic properties and the need for better investigations and to provide an update about the association of *SphK1* with hematological malignancy.

Materials and Methods

Protocol Registration

This systematic review and meta-analysis was first registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42021293661. It was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA 2020 checklist is given in Supplementary Tables S1a & S1b.

Search Strategy and Articles Selection

Electronic databases such as PubMed, Scopus, Embase, and OVID were used to identify the eligible studies published till February 2024. An extensive search strategy was conducted by using the keywords and medical subject heading (MeSH) terms: "Sphingosine kinase 1" OR "*SphK1*" OR "SK1" AND "Lymphoma" OR "Leukemia" OR "Multiple Myeloma". A summary of the search strategy is given in Supplementary Table S2. In databases, language and year of publication were not restricted while searching for articles. All searched articles were exported to the citation management tool (Zotero) and duplicate articles were then removed followed by relevant article filtration. Review articles, abstracts, case reports, and non-English language articles were excluded whereas full-text articles, mini-articles, and commentary or letters were then reviewed according to the predefined inclusion and exclusion criteria. Additionally, attempts were made to obtain papers that were not publicly available by getting in touch with the respective authors.

Inclusion Criteria

For the systematic review, studies were eligible to be included if they were: (1) Case-control studies (Hematological malignancy patient i.e., lymphoma, multiple myeloma, and leukemia as cases and healthy participants as control); (2) Studies reporting about *SphK1* expression; and (3) Detection technique i.e., PCR, immunohistochemistry (IHC), chromatography, western blot (WB), northern blot and southern blot.

For meta-analysis, studies with sufficient *SphK1* association data to compute (1) Odds ratio (OR) with 95% Confidence Interval (CI) and; (2) Standardized mean difference (SMD); with 95% CI were incorporated.

Exclusion Criteria

Studies were excluded if they were: (1) cell-line, animal, and insilico studies; (2) other than hematological malignancy disease or co-morbidities patients; (3) *SphK1* not reported or if reported but detection method not informed; and (4) non-availability of data to calculate OR and SMD.

Data Extraction and Quality Assessment

The following data were extracted from the identified eligible studies: (1) First author's last name; (2) Year of publication; (3) Country where the study was conducted; (4) Type of diagnosis; (5) Number of participants enrolled in the study (6) Type of sample (7) Techniques to quantify *SphK1*; and (8) Kind of *SphK1* expression. Demographic details would have been retrieved but due to the unavailability of data, the details were not extracted.

SM, MM, and TG had done the literature search. VU, ST, and SK clarified any ambiguities in the articles. The corresponding author M.B. cross-checked all these procedures.

SM, ST, and VU individually evaluated the quality of each eligible study using the Newcastle-Ottawa Scale (NOS) [36]. SH and MB double-checked the findings. The scale contains 9 questions categorized into 3 sections; (1) selection of cases and controls, (2) comparability, and (3) exposure. Scale has a maximum score of 9; if the study gets a score between 0-3 means low quality or high risk of bias, 4-6 means moderate quality or moderate risk, and 7-9 means high quality or low risk of bias.

Meta-analysis

Review Manager 5.4.1 software (Cochrane Collaboration, Copenhagen, Denmark) was used to find the association of *SphK1* in the experimental (hematological malignancy) and control groups (healthy participants). The strength of the *SphK1* association was estimated via OR along with a 95% CI.

For studies reporting dichotomous data (i.e., the number of participants in hematological malignancy and healthy group expressing *SphK1* were provided), OR with

a 95% CI was estimated by applying the random effect model using the Mantel-Haenszel statistical method. A random effect was employed since the background population varied even though all of the studies used the same study design.

In the case of continuous data, we would have estimated the SMD with a 95% CI. However, the data (mRNA expression data of *SphK1*) provided in the five studies were ineligible for SMD computation. Among these, four studies (Almejun et al.[24]; Liu et al. [40]; Petrusca et al. [38] and Salas et al. [34]) did not have an SD value to calculate SMD or a sample size of one, and because one study is insufficient to compute a forest plot, the study by LeBlanc et al.[32] was also excluded.

Finally, a graphical depiction of the outcomes from eligible studies-i.e., all the detailed information, including the OR of individual studies along with a 95% CI and a pooled summary effect bound by a 95% CI-was shown as a forest plot. Results with a $P < 0.05$ were considered significant. Moreover, the visualization of the funnel plot was used to determine the existence of publication bias among the articles that were incorporated into the meta-analysis.

Certainty of Evidence

The GRADE approach, which refers to the grading of recommendations, assessment, development, and evaluation through the use of GRADE pro GDT online software, was applied in the meta-analysis result to evaluate the certainty of the evidence [37]. The following GRADE criteria were used to grade the evidence quality: design of the study, risk of bias, results from inconsistency, indirectness, imprecision, and other considerations.

Results

Search Results

A total of 2209 articles were retrieved from the aforementioned four databases followed by the removal of 1423 duplicate articles and retained 786 articles for screening. On screening the titles and abstract, 733 articles were excluded, leaving 53 articles included for full-text review. Following a thorough assessment, 9 articles met the inclusion criteria for systematic review, with 44 articles being excluded based on predefined exclusion criteria outlined in Supplementary Table S3. A summary of searched results is depicted in a PRISMA flowchart Figure 1.

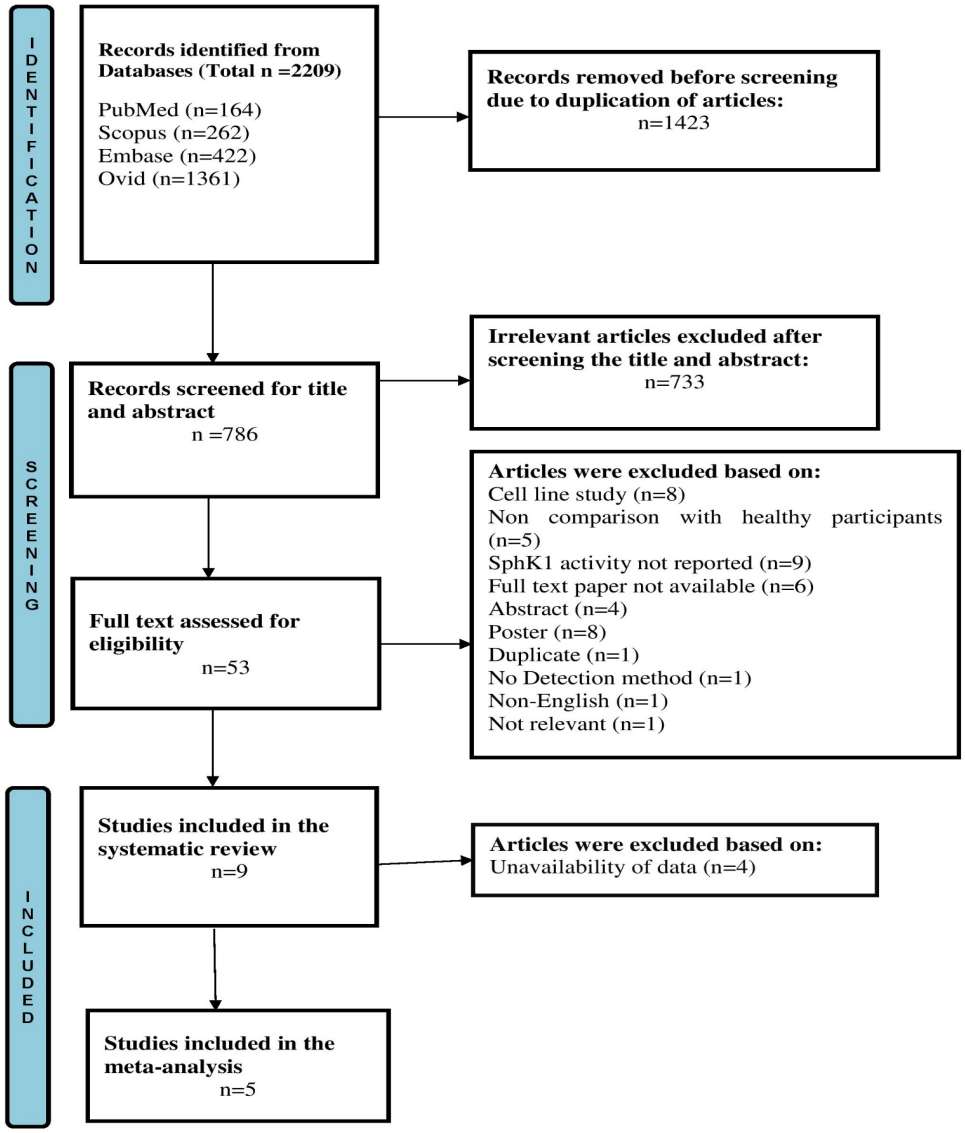

Figure 1. PRISMA Flowchart Depicting the Searched Study Selection Process

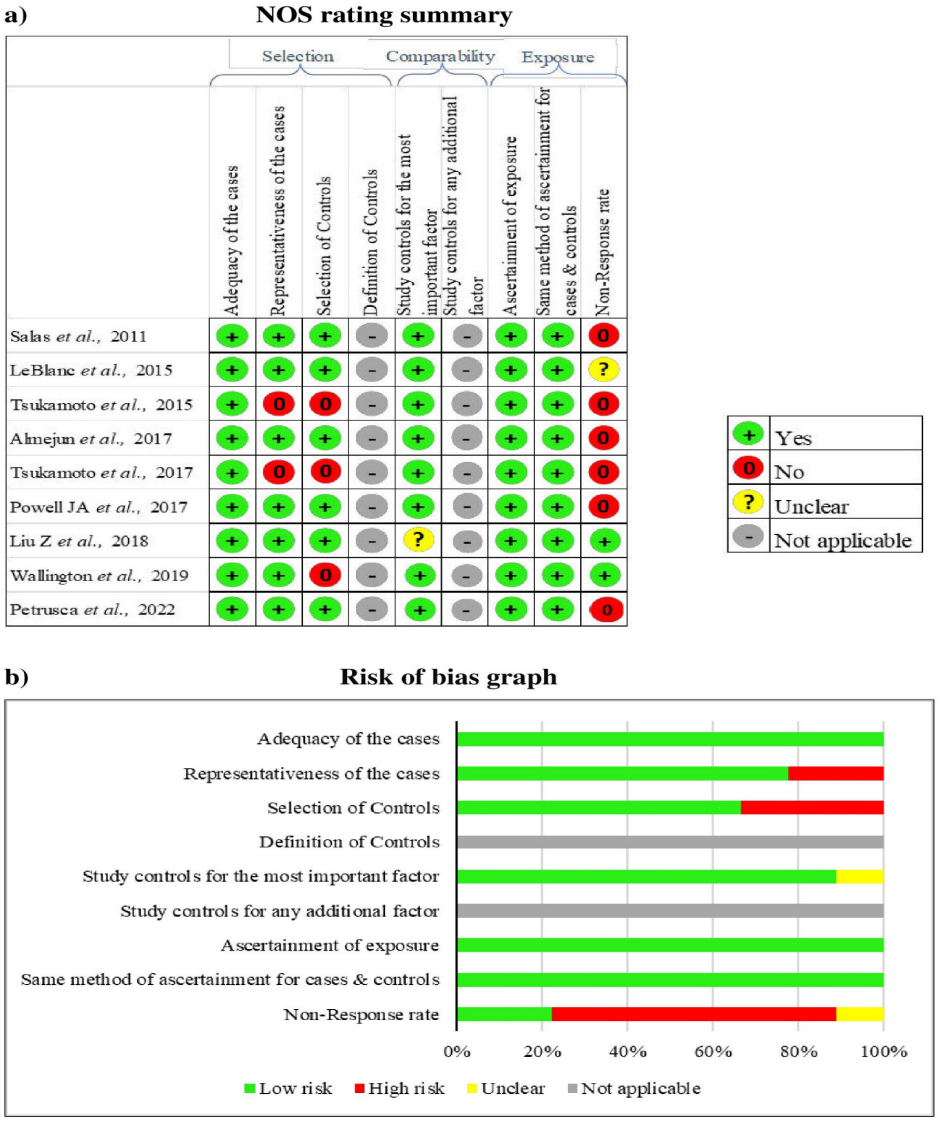

Figure 2. Quality assessment of the 9 Eligible Studies Using the Newcastle-Ottawa Scale. (a) NOS rating summary; (b) Risk of bias graph

Characteristics of the included studies and quality assessment

Among the 9 studies included in the systematic review, the distribution across various hematological malignancies was as follows: 2 studies each on chronic myeloid leukemia (CML) [34, 40], chronic lymphocytic leukemia (CLL) [24, 39], and multiple myeloma (MM) [30, 38], 1 study each on large granular lymphocyte leukemia (LGL) [32], acute myeloid leukemia (AML) [28], and acute lymphoblastic leukemia (ALL) [15]. Detection techniques such as qRT-PCR and western blot were reported in the included studies for evaluating the expression of *SphK1*. While two studies employed both qRT-PCR and western blot, the remaining 7 studies utilized either of these techniques for *SphK1* detection. Detailed characteristics and findings of all eligible studies are presented in Table 1.

The NOS rating for all 9 studies ranged from 4 to 6, and was considered to have a "moderate quality". A

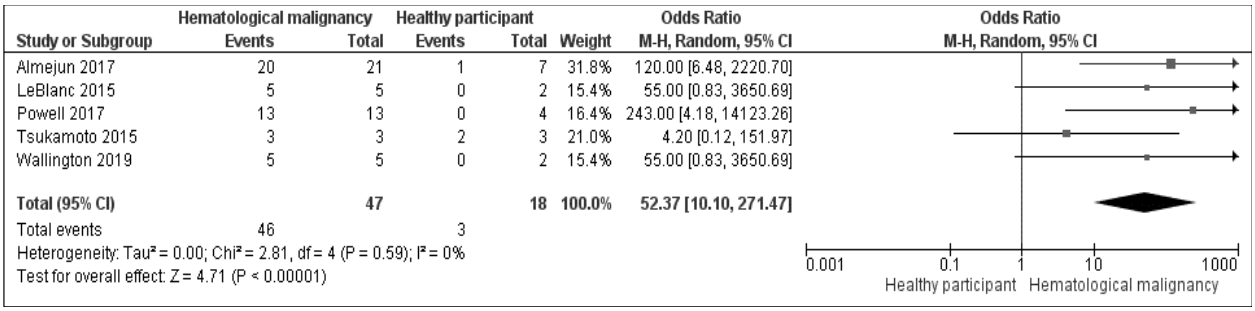

Figure 3. Forest Plot Showing the Pooled OR of SphK1

Table 2. Certainty of Evidence Assessment

Certainty assessment							No. of patients		Effect	Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cases	Controls	Relative (95% CI)	
5	observational studies	not serious	serious	not serious	not serious	strong association	47 cases 18 controls		OR 52.37 (10.10 to 271.47)	⊕⊕◯◯ Low

Table 1. Characteristics and Findings of the Eligible Studies Included in the Systematic Review

S. N.	Author	Published year	Country	Diagnosis	No. of participants in		Sample type	SphK1 Detection method	SphK1 Expression Type	Result of SphK1 detection in disease vs. control
					Disease Group	Control Group				
1	Salas et al. [34]	2011	USA	CML	1	1	MNC	qRT-PCR	mRNA	2.5-fold higher in DG than control
2	LeBlanc et al. [32]	2015	USA	LGL	8	8	NK cells	qRT-PCR	mRNA	Significantly increased in DG ($P < 0.05$)
					5	2		Western blot	Protein	At protein levels, 3-fold increased in DG
3	Tsukamoto et al. [30]	2015	Japan	MM	3	3	PBMC	Western blot	Protein	Markedly increased in DG
4	Almejun et al. [24]	2017	Argentina	CLL	30	10	B cells	qRT PCR	mRNA	Higher in DG (Statistically significant)
					21	7		Western blot	Protein	Higher expression in DG
5	Tsukamoto et al. [39]	2017	Japan	CLL	24	-	B cells	Western blot	Protein	Overexpressed in DG
6	Powell et al. [28]	2017	Australia	AML	13	4	MNC	Western blot	Protein	Elevated in DG
7	Liu et al. [40]	2018	China	CML	68	68	-	qRT PCR	mRNA	Significantly upregulated in DG ($P < 0.001$)
8	Wallington et al. [15]	2019	Australia	B- lineage ALL	5	2	BM	Western blot	Protein	Increased expression in DG
9	Petrusca et al. [38]	2022	USA	MM	7	3	BM	qRT PCR	mRNA	Increased in DG but statistically not significant

Abbreviations: CML, Chronic Myeloid Leukemia; LGL, Large granular lymphocytic leukemia; MM, multiple myeloma; CLL, Chronic lymphocytic Leukemia; AML, Acute myeloid leukemia; ALL, Acute lymphoblastic leukemia; qRT-PCR, Real-Time Quantitative Reverse Transcription Polymerase Chain Reaction; MNC, Mononuclear cells; NK, Natural killer; PBMC, Peripheral blood mononuclear cells; BM, bone marrow; DG,Disease Group

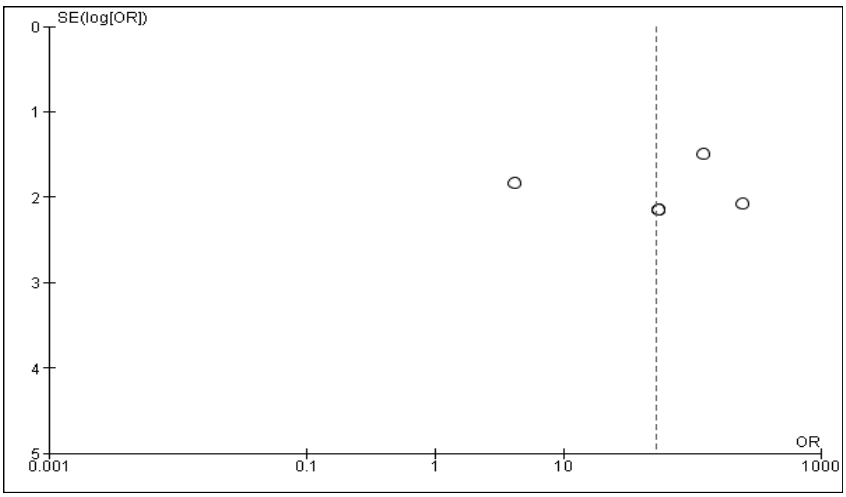

Figure 4. Funnel Plot Showing Publication Bias

summary of NOS rating and risk of bias graph is presented in Figure 2.

Meta-analysis

Six out of nine studies reported protein expression of *SphK1* by the WB technique (dichotomous data). Five of those studies (LeBlanc et al. [32]; Tsukamoto et al. [30]; Almejun et al.[24]; Powell et al. [28]; and Wallington et al. [19]) were eligible for meta-analysis to estimate OR, and one study by Tsukamoto et al. [30] was not included due to the unavailability of participant's numbers. The odds of *SphK1* were found to be significantly positive or higher in patients with hematological malignancy than in healthy participants, with a pooled OR (95% CI) of 52.37 (10.10 to 271.47) and P = 0.00001 (Figure 3).

The graph of the funnel plot for determining the existence of publication bias was symmetric and did not indicate any publication bias in favor of the studies reporting higher OR (Figure 4).

Certainty of Evidence

GRADE findings showed a low certainty of evidence for the meta-analysis evaluating the association of Sphk1 with hematological malignancy (Table 2).

Discussion

The current systematic review kept 9 studies (159 hematological malignancies and 99 healthy participants) for full-text review and ultimately retained 6 studies for meta-analysis to achieve the aim of evaluating the association between *SphK1* and hematological malignancies. Analyzing the OR meta-analysis result of the studies individually, all 5 studies [15, 24, 28, 30, 32] have OR > 1, but three studies [15, 30, 32] have CI values that crossed the line of no effect despite having OR > 1. This makes them less significant individually. However, since the pooled OR from 47 hematological malignancy participants and 18 healthy participants, is greater than 1 with P = 0.00001, we can conclude that *SphK1* is significantly associated with hematological malignancy. In terms of the quality of evidence, the level of certainty was found low due to inconsistent results. Inconsistency is due to the heterogeneity among the hematological malignancy types.

Possible explanations of the results in the context of other findings

Activation or deactivation of enzymes and proteins is always a crucial event in almost all inflammatory pathways. Therefore, researchers have always prioritized targeting the right enzymes or proteins in inflammation. There is massive evidence of considering *SphK1* as a key target and elucidating the pathways through which *SphK1* participates in chronic inflammatory diseases such as cardiovascular disease, alzheimer's disease, cancer, etc. [6-7,41]. Due to the dearth of studies detailing the mechanisms via which *SphK1* contributes to malignancy, the current systematic review and meta-analysis only seek to determine the association of *SphK1* outcomes in malignancy from case-control studies. However, *SphK1*'s involvement in activating different dysregulated pathways and its contribution to disease pathogenesis can be supported by different clinical, cell line, and animal studies.

1. In A case-control study conducted in 85 colorectal cancer (CRC) tissue samples and adjacent normal mucosa, an increased *SphK1* protein (67 out of 85) and mRNA expression in CRC samples than normal samples had been reported. Additionally, IHC analysis revealed that CRC tissue had greater expression of nuclear *SphK1* (65 out of 85 samples). qRT-PCR analysis was also carried out in human CRC cell lines, where a higher *SphK1* level was discovered and elucidated the role of *SphK1* in cell proliferation and invasion [42].

2. One study included in our review elucidated that *SphK1* suppression could cause apoptosis in AML. Since *SphK1* induces MCL1, AML cells survive when it is activated [28]. This could be supported by another study performed in CML cell lines, which reported that *SphK1* expression up-regulated MCL-1 expression and thereby silencing *SphK1* could result in cell death [29]. Apart from MCL-1 pathway, *SphK1* stimulates the PI3K/Akt, NF-kB, JAK/ STAT, and ERK pathways [31, 43-45].

Overexpression of *SphK1* is also linked to autophagy and chemoresistance. A study in non-small cell lung cancer (NSCLC) discovered the elevated expression of *SphK1* by preventing apoptosis via activation of the PI3K/Akt/NF-kB pathway and thus promotes chemoresistance [46]. A similar study on bladder cancer informed that increased *SphK1* leads to cisplatin failure in both cell lines and the patient's tumor through activation of the NONO/Stat3 pathway [47].

3. An Invivo investigation in 2017 employed 3 different animal models and supported *SphK1*'s association with colon cancer promotion. Initially, when exposed to colon carcinogen azoxymethane, 17 out of 28 *SphK1* Knockout (KO) mice dramatically reduced the tumor growth compared to C57BL/6 wild-type (WT) mice (27 out of 28 mice). Second, when HT-29 cells were subcutaneously implanted into xenograft models, *SphK1* over-expression mice developed tumors earlier (at 18 days) and in a bigger volume than GFP control nude mice (at 21 days). Lastly, transgenic mice were created based on the tet-on system. *SphK1* over-expression in intestinal epithelial cells mice had increased tumor growth than control WT mice [48].

Considering the above findings in the context of our results, it has confirmed our aim to evaluate the association between *SphK1* and hematological malignancy. Furthermore, a prior systematic review and meta-analysis that examined the connection between *SphK1* and different cancers found a significant association of *SphK1* with cancer and confirmed that this association affected 5year overall survival of cancer patients [49]. A recent meta-analysis on this subject also revealed that *SphK1* expression levels are linked with a patient's worst prognosis for solid tumors [22].

Implications and Limitations

Analyzing *SphK1* expression levels in patients could provide early diagnostic and better understanding of the disease; therefore, *SphK1* could be recognized as a potential diagnostic biomarker. In addition, this can help in the identification of chemo-resistant or chemo-sensitive tumor patterns. Since many cancer patients develop resistance towards anticancer agents, hence early assessment of *SphK1* expression in hematological malignancy patients could help to provide a better targeted and personalized treatment.

Several limitations exist in our study. First, due to inclusion criteria, many articles published in languages other than English were excluded. This might have led to language prejudice. Second, some studies were ineligible for meta-analysis as they had a missing participant number in either the control or cases group, and some studies failed to provide SD values. Third, the *SphK1* detection technique is different in each type of hematological cancer. Fourth, although *SphK1*'s association with hematological malignancy was found significantly positive, the correlation was limited to elucidate *SphK1*'s role through mechanistic insights. Lastly, the study was limited to case-control studies due to the lack of other epidemiological studies for which we were unable to evaluate whether *SphK1* expression might vary over time, and the prognosis of hematological malignancy with *SphK1* association was not observed.

In conclusion, the current systematic review and meta-analysis confirmed the positive association of *SphK1* with hematological malignancy based on the clinical findings. As a result, our findings indicated and supported the possibility that *SphK1* could serve as a therapeutic biomarker to combat malignancy in blood.

Although we did discover an association between *SphK1* and hematological malignancy, the association was not able to assess *SphK1*'s function through mechanistic insights. Therefore, employing mechanistic insights, more research must be done on *SphK1*'s role in hematological malignancy.

Author Contribution Statement

SM, ST, and MB designed the experiments; SM, MM, and TG searched the literature. SK, ST, and VU helped in clearing all the doubts during screening and data extraction; SM, VU, and ST discussed the results and strategy; MB and SH supervised, directed, and managed the study; SM and MB drafted the manuscript; and SM, ST, VU, SK, MM, TG, MB, and SH approved the final version of the manuscript.

Acknowledgements

If it was approved by any scientific Body/ if it is part of an approved student thesis

This systematic review and meta-analysis do not require approval from any scientific body, nor are they part of a student thesis.

Availability of data

Provided as supplementary data.

Ethical approval

The study did not involve any human participants or any animal models. Hence, no ethical approval is required.

Conflict of Interest

None.

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