Systematic Review and Meta-Analysis of Lysine-Specific Demethylase 1 Expression as a Prognostic Biomarker of Cancer Survival and Disease Progression

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Abstract

Background: Numerous studies on the prognostic significance of lysine-specific demethylase 1 (LSD1) up-regulation in tumors have different outcomes. The inconsistency originated from various studies looking into the association between LSD1 and tumor cells has prompted the decision of this quantitative systematic review to decipher how up-regulated LSD1 and overall survival (OS) or recurrence-free survival (RFS) or disease-free survival (DFS) are linked in tumor patients.

Methods: Articles were searched from online databases such as Embase, *Web of Science Core*, PubMed, Google Scholar, and Scopus. The extraction of the hazard ratios (HR) with their 95% confidence intervals (*CIs*) was attained and survival data of 3151 tumor patients from 17 pieces of related research were used for this meta-analysis.

Results: To shed light on the link between LSD1 up-regulation and the prognosis of diverse tumors, the pooled hazard ratios (HRs) with their 95% confidence intervals (*CIs*) were determined. In this meta-analysis, it was observed that LSD1 up-regulation is linked with poor OS (HR = 2.08, 95% *CI*: 1.66–2.61, P < .01) and RFS (HR = 3.09, 95% *CI*: 1.81–5.26, P < .01) in tumor patients. However, LSD1 up-regulation was not linked to DFS (HR = 1.49, 95% *CI*: .83–2.69, P = .18) in tumor patients. The subcategory examination grouped by tumor type and ethnicity showed that LSD1 up-regulation was linked with a poor outcome in the esophageal tumor and hepatocellular carcinoma and Asian patients, respectively. For clinical-pathological factors, up-regulated LSD1 was significantly linked with Lymph node status.

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Conclusion: Despite the shortfall of the present work, this meta-analysis proposes that LSD1 up-regulation may be a prognostic biomarker for patients with tumors including esophageal tumors and hepatocellular carcinoma. We propose that large-scale studies are vital to substantiate these outcomes.

Introduction

One of the leading causes of death worldwide is tumor.[1] As a result of that, there has been a significant enhancement in the investigation, treatment methods and good maintenance practices on cancer, but unfortunately, the prognosis of cancers remains very stumpy. The reason for this could be the limited detection approaches for cancer patients in their initial phases and also the ever-increasing recurring nature of cancers. According to Cui et al,[2] the vital means of enhancing the prognosis of cancers are timely diagnosis and remedy. However, the sensitivity and specificity of a lot of tumor biomarkers are not adequate. Hence, it is of inordinate significance to ascertain novel biomarkers to forecast the prognosis and therapy targets for tumors.

Lysine-specific demethylase 1 is a monoamine oxidase homolog, which precisely removes methyl groups of H3K4/H3K9, thus triggering activation or suppression of genes.[3-5] Lysine-specific demethylase 1 control of gene expression has been revealed to be vital to manifold procedures together with organogenesis and stem cell differentiation.[6,7] Lysine-specific demethylase 1 plays a key role in non-histone proteins by getting rid of mono- and di-methylation which could be linked to tumor progression.[8] According to Yang et al,[9] the demethylation of HIF-1α, E2F1, DNMT1, and STAT3 by LSD1 has to make LSD1 the controller of cell cycle arrest and the regulator of cancer cell proliferation and angiogenesis as well as remolding of chromatin. Lysine-specific demethylase 1 minimizes the reaction of p53 and 53BP1; a tumor suppressor gene, by eliminating a methyl group from p53K370me2, thereby suppressing the role p53.[10] Thus, LSD1 functions as a demethylase of non-histone protein. Lysine-specific demethylase 1 functions as a transcription co-repressor by demethylating H3K4me2/1 and shaping chromatin into a repressive conformation through diverse complexes formed by LSD1 and other numerous proteins. Through the development of HOTAIR/PCR2 complexes as well as the complexes of HP1/SU(VAR)3–9, the repressive conformation could stimulate gene silencing. Nucleosome remodeling through NuRD complexes[11] and controlling of the stem cell properties through TLX and RCOR2 complexes[12] are done by the repress expression of specific genes in the form of a core-BRAF35 or CoREST complexes.[13] Moreover, LSD1 acting as a transcriptional co-activator enhanced the demethylation of H3K9me2/1. Again, replication control, the propagation of heterochromatin, and imprinting are intermediated by LSD1. This could stimulate the transcription of genes in prostate and breast tumors through relating with androgen and estrogen receptors.[14]

The over-expression of LSD1 in a lot of tumor cells has been well documented.[15,16] LSD1 up-regulation has been revealed to be stalled in several processes of malignancies, such as proliferation, invasion and cell cycle acceleration.[17] Aberrantly, the up-regulation of LSD1 stimulates tumorigenesis by regulating chromatin through chromatin remodeling and aggregation.[18] Also, the cell cycle of cancer is affected,[19] by the up-regulation of LSD1 that can result in inhibition of p53 task by inhibiting the reaction between TP53BP1 and p53 thus, p53 binding protein 1,[20] which then promotes tumor growth, invasion and metastasis by affecting the methylation/demethylation process.[10,21,22] Hence, LSD1 has become an important therapeutic target for cancer therapy.[5,23]

Some researchers assessing the prognostic significance of LSD1 in numerous tumor cells asserted that over-expression of LSD1 can be linked to poorer results among tumor patients.[21,24] However, results from other works are inconsistent.[25] Consequently, the relationship between LSD1 up-regulation and OS/RFS/DFS through diverse tumors remains contentious. Because of the numerous limitations that come with single studies, our meta-analysis was carried on to decipher the relation between up-regulated LSD1 and the prognosis of tumor patients.

We are motivated to conduct this meta-analysis because the only meta-analysis involving up-regulated LSD1 conducted by Wu et al[26] had only 9 included studies and worked on the association between up-regulated LSD1 and OS. However, the current study involved the link between up-regulated LSD1 and OS or RFS or DFS with 17 included studies. Again, the link between up-regulated LSD1 and clinical pathological factors was also scrutinized.

Methodology

Registration of the Study

The protocol for this systematic review was registered on INPLASY and is available in full on inplasy.com (https://doi.org/10.37766/inplasy2021.8.0011). The registration number is INPLASY202180011 and the DOI is 10.37766/INPLASY2021.8.0011. The Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) was followed to develop this protocol.[27]

Literature Exploration and Assortment Conditions

Two reviewers (AC and DJ) sampled peer-reviewed articles published up to September 2020. They carried on a search in Cochrane Library, Web of Science Core, Wanfang Database, PubMed, Embase, Google Scholar, Scopus, and China National Knowledge Infrastructure to recognize pertinent researches. The search screened studies with the following keywords: "LSD1 and tumor," "neoplasm and carcinoma," "malignant and survival," and "prognosis and prognostic". The recovered studies references were also examined for additional suitable works to prevent the loss of connected studies.

Population type. The patient with tumors considered having up-regulated LSD1. Gender and tumor type are not restricted.

Inclusion and Exclusion Conditions

The parameters that were considered before the works were involved in our meta-analysis were: (1) Studies with human tissues considered to have LSD1 up-regulation. (2) Tumor cell confirmation must be done pathologically or histologically. (3) The estimated link between up-regulated LSD1 and survival must be determined. (4) To assess the OS or RFS or DFS of tumor patients, studies should have adequate available data that will aid in the evaluation of the various HRs and their 95% *CIs* or odds ratio (OR). The exclusion conditions involved (1) Articles that have no data such as letters, case reports, reviews and conference abstracts. (2) Papers in which applicable data may not be hauled out from. For papers with repeated data, the one with the most complete work was involved in the analysis. This work was done by EYC and DKE via the risk of bias tool developed by the Cochrane Collaboration.[28] Disagreement was resolved via discussion or consultation with a third reviewer (H-ML).

Haul out of Appropriate Data

For this meta-analysis, data were assessed and haul out from the suitable works using the procedures of a vital review list of the Cochrane Centre suggested by Meta-analysis of Observational Researches in Epidemiology.[29] Information extracted from each article were: the name of the first author, the year of publication, the country, ethnicity, HRs with their 95% *CIs*, a technique used, the type of tumor, and the number of patients employed in the study. In situations where the HRs with their 95% *CIs* were not directly provided, they were estimated from available data such as observed deaths/tumor recurrences[30] and Kaplan–Meier curves using previously described approaches.[31,32] For the relationship between the up-regulated LSD1 and OS or DFS or RFS, the HRs and 95% *CIs* should be considered. Clinical pathological factors include age, gender, lymph node status, tumor differentiation, tumor stage, vascular invasion, and tumor grade. The value of involved articles was evaluated using the

Newcastle Ottawa Scale (NOS),[33] high-quality studies were considered to have scored ≥ 7.

Missing Data or Information

Two reviewers (PW and DKE) contacted some authors (corresponding authors) of articles via email for additional information about some missing data as stated in the Cochrane handbook for systematic reviews. The papers with missing or unclear data that sufficient information was not obtained from the original authors were excluded from this study. The probable impact of inadequate data on the review results will be taken into account in the discussion section.

Valuation of Reporting Biases

Our study has an adequate number of included papers (more than 10 studies) that are presented in the meta-analysis. So the reported bias was assessed using the funnel plot.

Statistical Analysis

Base on the link between LSD1 up-regulation and OS/RFS/DFS of tumor patients, we evaluated the HRs and their 95% *CIs*. The heterogeneity amongst studies was estimated using chi^2 and I^2 statistics. For the I^2 test, the criteria for heterogeneity were as follows: $I^2 < 25\%$ shows no heterogeneity; moderate heterogeneity considered being 25%–75%; high heterogeneity was considered to be $I^2 > 75\%$. The estimation of the publication bias was achieved through Begg's funnel plot. Data were analyzed using soft RevMan v.5.3, which is considered significant at P < .05.

Subgroup Analysis

There was no pre-subgroup analysis plan for this study. Subgroup analysis was conducted since there is heterogeneity in the study.

Results

Literature Search

Initially, we assessed 89 articles obtained from the literature search. The abstraction of replicas and appraisal of abstracts and titles further screened the articles, 43 whole articles were assessed. However, only 27 articles met the inclusion conditions. Subsequently, 10 articles were left off due to an inadequate amount of data. Accordingly, 17 articles were used in our meta-analysis, Figure 1.

Study Characteristics

We haul out 17 involved articles having a total sample size of 3151 patients for this meta-analysis with 407 patients, being the highest sample size and 17 patients being the lowest sample size. The
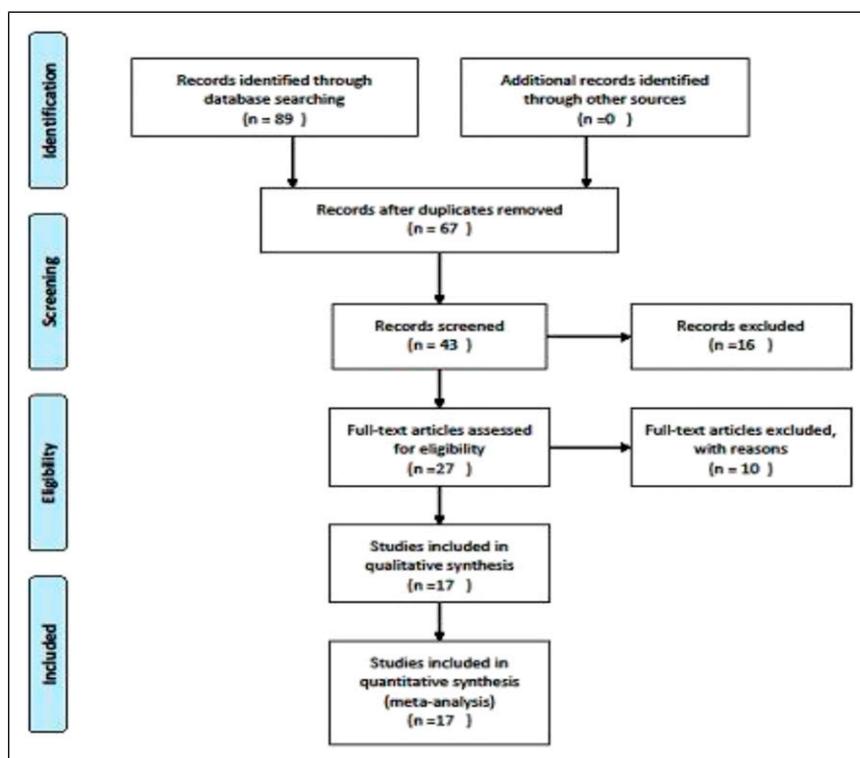
Figure 1. Flow diagram of the study selection.

involved tumor types include breast cancer, clear cell renal cell carcinomas, colorectal cancer, esophageal cancer, human melanomas cervical cancer, tongue cancer, non-small-cell lung cancer, and hepatocellular carcinoma. Fourteen of the articles were performed among Asians, three among Caucasians. All studies assessed the expression of LSD1 by immunohistochemistry (IHC). Among these studies, 15 articles were on OS, 5 articles on DFS, and 2 articles on RFS. HR with their 95% *CI* was stated directly in 12 articles, four studies have their HR with 95% *CI* extrapolated from survival curves and one study was obtained from available data. NOS scores ranged from 6 to 9. The detailed features of these eligible articles are listed in Table 1.

In clinical-pathological factors, 5 articles were acknowledged for the link between age and cancer prognosis, 10 articles for gender, 6 articles for lymph node status, 2 articles for tumor differentiation, 10 studies for the tumor stage, 3 studies for vascular invasion, and 7 studies for tumor grade Table 2.

Up-Regulated LSD1 and OS

A total of fifteen articles comprising of 2785, patients gave suitable data OS examination. As a result of statistical significance of heterogeneity among these studies ($I^2 = 53\%$, P = .008), the random-effect model was used to estimate the pooled HR and corresponding 95% *CI* because heterogeneity was found ($I^2 = 53\%$, P = .008). The pooled HR was 2.08 with their 95% *CI* being (1.85–6.90). Thus, the result established

that up-regulated LSD1 was substantially linked with poor OS in patients with cancers Figure 2.

Up-Regulated LSD1 and DFS

A total of 5 articles, comprising of 1031 patients, gave suitable data for DFS investigation. Due to the statistical significance of heterogeneity among these studies ($I^2 = 74\%$, P = .004), the random-effect model was approved to evaluate the pooled HR and corresponding 95% *CI*. The result indicated that there was no substantial link between up-regulated LSD1 and poor DFS (HR = 1.49, 95% *CI*: .83–2.69, P = .18) Figure 3.

Up-Regulated LSD1 and RFS

A total of 2 articles, comprising 517 patients, gave suitable data for the RFS examination. The fixed-effect model was used since no palpable heterogeneity was establish ($I^2 = 0\%$, P = .74). The HR was 2.57 (95% *CI*: 1.81–5.26, P < .001), which showed a significant link between up-regulated LSD1 and poor RFS Figure 4.

Subgroup Analysis

Patients were grouped into their different conditions and subgroup analysis was conducted. Subgroup analysis conducted in terms of tumor type indicated that up-regulated

Table 1. Main characteristics and results of the eligible studies

Study (year)	Tumor type	Ethnicity	Number of patients	Outcome	HR estimate	HR	95% CI	NOS
Zhu 2019 [17]	Clear cell renal cell carcinomas	Asian	358	OS/RFS	Reported	3.571	1.846–6.908	9
Carvalho 2018 [34]	Colorectal cancer	Caucasian	207	DFS	Reported	.486	.251–.940	8
Liu 2015 [35]	Endometrioid endometrial adenocarcinoma	Asian	301	OS/DFS	Reported	3.36	1.15–9.83	7
Chen 2015 [36]	Epithelial ovarian Cancer	Asian	407	OS	Reported	2.808	1.131–6.967	7
Kim 2019 [37]	Hepatocellular carcinoma	Asian	303	OS/DFS	Survival curve	2.16	1.31–3.56	9
Derr 2014 [25]	Breast cancer	Caucasian	261	OS	Reported	1.182	.935–1.495	7
Yuan 2015 [24]	Tongue cancer	Asian	67	OS	Reported	3.908	1.238–12.339	7
Lin 2014 [38]	Esophageal cancer	Asian	135	OS	Reported	1.645	1.182–2.5	7
Chen 2014 [39]	Esophageal cancer	Asian	103	OS	Reported	1.34	.69–2.6	8
Nagasawa 2015 [40]	Breast cancer	Asian	159	RFS	Reported	.1426	.04534–.8858	8
Lv 2012 [21]	Non-small-cell lung cancer	Asian	80	OS	Survival curve	2.49	1.51–4.08	7
Zhao 2012 [41]	Hepatocellular carcinoma	Asian	198	OS/DFS	Reported	2.456	1.234–3.932	7
Beilner 2020 [42]	Cervical cancer	Caucasian	250	OS	Reported	2.071	1.046–4.099	8
Kosumi 2016 [43]	Esophageal cancer	Asian	17	OS/DFS	Reported	4.08	1.67–11.5	8
Miura 2014 [44]	Human melanomas	Asian	63	OS	Available data	.689	.083–5.715	6
Ding 2013 [45]	Colon cancer	Asian	108	OS	Survival curve	1.74	1.03–2.94	7
Yu 2013 [22]	Esophageal cancer	Asian	134	OS	Survival curve	2.42	1.43–4.07	7

Abbreviation: HR: hazard ratios; OS: overall survival; CI: confidence intervals; RFS: recurrence-free survival; DFS: disease-free survival.

LSD1 was substantially linked with poor outcome in the esophageal cancer HR = 1.97, 95% CI: 1.36–2.87, $P < .001$) with no substantial heterogeneity (I^2= 44%, P = .14) and hepatocellular carcinoma (HR = 2.26, CI: 1.51–3.36, $P < .001$) with no significant heterogeneity (I^2 = 0, P = .77). Again, up-regulated LSD1 was not substantially linked with the breast tumor (HR = 1.81, 95% CI: .62–5.27, P = .27) with no significant heterogeneity (I^2 = 74%, P= .05). Also, there was a significant link between up-regulated LSD1 and prognosis in other tumors such as clear cell renal cell carcinomas, tongue cancer, cervical cancer, non-small-cell lung cancer, human melanomas and epithelial ovarian cancer (HR = 2.01, 95% CI: 1.27–3.19, P = .003) with significant heterogeneity (I^2 = 68%, P = .001). Subgroup examination conducted in terms HR estimate showed that up-regulated LSD1 was significantly linked with poor prognosis in reported category (HR = 1.98, 95% CI: 1.41–2.78, $P < .001$) with substantial heterogeneity (I^2 = 78.0%, $P < .001$) and survival curve category (HR=2.19, 95% CI: 1.69–2.83, $P < .001$) with no substantial heterogeneity (I^2 = 0%, P = .077). Likewise, up-regulated LSD1 was

linked with poor prognosis in the subcategory of sample size. For sample size ≤ 200 (HR = 208, 95% CI: 1.68–2.58, $P < .001$) and sample size > 200 (HR2.14, 95% CI: 1.45–3.14 $P < .001$).The subgroup examination conducted in terms of ethnicity showed that that up-regulated LSD1 was substantially linked with poor prognosis in Asians (HR=2.20, 95% CI: 1.84–2.63, $P < .001$) but not substantially linked with poor prognosis in Caucasians (HR=1.07, 95% CI: .56–2.05, P = .84) Table 3.

Up-Regulated LSD1 With Prognosis Factors

The link between up-regulated LSD1 and prognosis factors has been studied. These include tumor grade (T3–T4 vs T1–T2), vascular invasion (present vs absent), tumor stage (III–IV vs I–II), tumor differentiation (poor v well), lymph node status (yes vs no), gender (male vs female), and age (≤ 60 vs > 60). It was observed from the study that up-regulated LSD1 significantly correlated with lymph node status (yes vs no) (OR = 3.37, CI: 1.47–7.75, P = .004). However, up-regulated LSD1

Table 2. Lysine-Specific Demethylase 1 expression with clinical-pathological parameter

| Study	Age		Gender		Tumor size		Lymph node status		Tumor differentiation		Tumor stage		Vascular invasion		Tumor grade	
	≤60	>60	M	F	≥3.5	<3.5	Yes	No	Poor	Well	IV–III	I–II	Present	Absent	T4–T3	T1–T2
Zhu 2019 [17]	—	—	161/93	63/41	—	—	—	—	—	—	16/1	208/133	—	—	42/19	184/115
Carvalho 2018 [34]	—	—	115/-	96/-	—	—	—	—	—	—	28/-	30/-	—	—	—	—
Liu 2015 [35]	74/36	73/23	—	—	—	—	18/1	129/58	—	—	18/3	129/56	56/6	91/53	—	—
Chen 2015 [36]	21/19	26/30	—	—	.	—	65/6	16/9	—	—	60/6	21/9	—	—	29/5	52/10
Kim 2019 [37]	—	—	166/61	66/10	—	—	—	—	51/5	49/23	31/1	32/7	—	—	31/2	30/8
Derr 2014 [25]	—	—	—	—	—	—	236/-	224/-	—	—	—	—	—	—	—	—
Yuan 2015 [24]	24/14	18/7	32/14	19/7	—	—	12/37	2/52	—	—	25/11	17/10	32/19	10/2	—	—
Chen 2014 [39]	6/34	8/55	10/65	4/24	13/52	1/37	11/16	17/26	—	—	8/26	6/63	—	—	—	—
Lv 2012 [21]	13/22	14/21	20/31	8/11	—	—	—	—	—	—	—	—	—	—	—	—
Zhao 2012 [41]	—	—	58/43	54/43	.	—	—	—	—	—	86/31	26/55	—	—	38/1	72/85
Beilner 2020 [42]	—	—	—	—	—	—	—	—	—	—	44/206	112/138	—	—	20/230	163/87
Kosumi 2016 [43]	—	—	53/47	7/6	—	—	—	—	—	—	20/11	40/40	29/9	24/37	25/11	35/40
Miura 2014 [44]	—	—	20/4	33/10	—	—	21/4	32/10	—	—	—	—	—	—	—	—
Ding 2013 [45]	—	—	42/23	30/13	—	—	—	—	—	—	42/13	30/23	—	—	23/9	49/17
Yu 2013 [22]	34/35	21/36	41/57	14/14	—	—	25/19	30/52	4/11	19/27	—	—	—	—	—	—
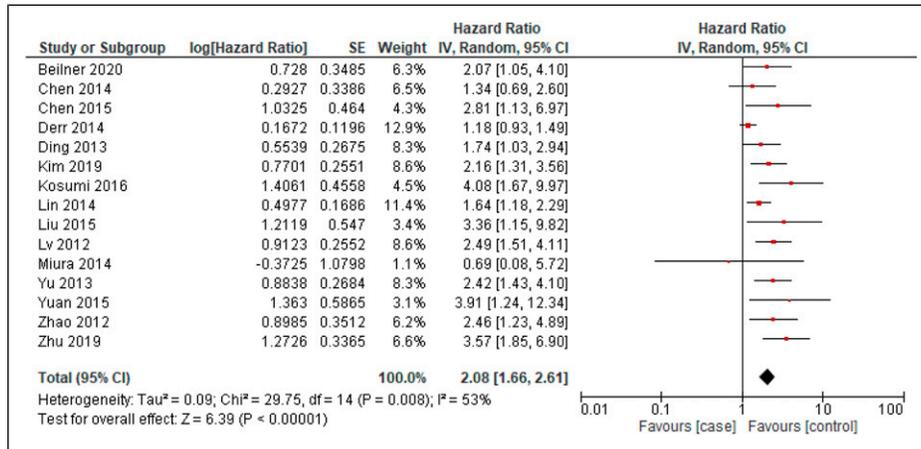
Figure 2. Forest plots for the link between up-regulated lysine-specific demethylase 1 and overall survival. Note: SE, log(Hazard Ratio) and Weights are from random effects analysis.
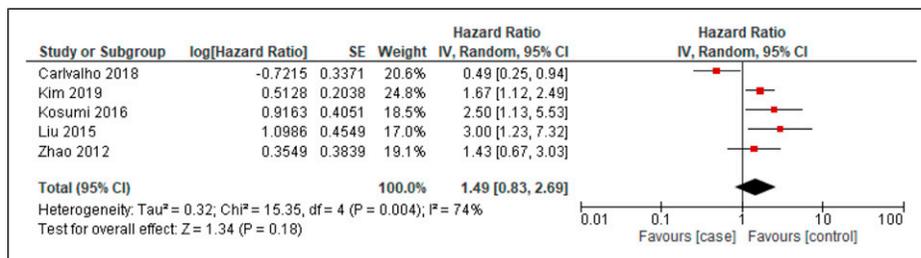

Figure 3. Forest plots for the link between up-regulated lysine-specific demethylase 1 and disease free survival. Note: SE, log(Hazard Ratio) and Weights are from random effects analysis.
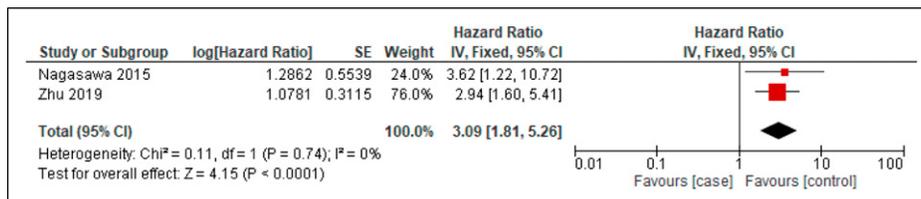

Figure 4. Forest plots for the link between up-regulated lysine-specific demethylase 1 and recurrence free survival. Note: SE, log(Hazard Ratio) and Weights are from fixed effects analysis.

was not significantly linked to prognosis factors, such as tumor grade (T3–T4 vs T1–T2) (OR = 1.46 CI: .30–7.12, P = .64), vascular invasion (present vs absent) (OR = 2.48 *CI*: .62-9.85 P = .20), tumor stage (III–IV vs I–II) (OR = 2.50, *CI*: .97–6.47, P = .06), tumor differentiation (poor vs well) (OR = 1.63, CI: .18–14.41, P = .66), gender (male vs female) (OR = .70, *CI*: .36–1.36, P = .29), and age (≤ 60 vs > 60) (OR = 1.03 *CI*: .72–1.46, P = .88) Table 4.

Publication Bias

There was no palpable evidence of asymmetry from the shape of the funnel plot Figure 5, demonstrating that there was no substantial publication bias in the meta-analysis for OS. However, as a result of limited included articles for DFS and RFS, we did not evaluate the publication bias as it will be unreliable.[46]

Up-Regulated LSD1 Stimulates the Epithelial–Tomesenchymal Transition

Irregular LSD1 deed is comprehensively branded in numerous tumor cells. The mechanism of LSD1 in the stimulation of tumor progression is not influenced by the suppression of controllers of the cell cycle. For instance, apoptosis is repressed by LSD1 through an exceptional non-histone protein,

Table 3. Subcategory examination of pooled HR for OS/DFS/RFS.

Category	Number of Studies	Number of Patients	P-value	Pooled HR (95% CI)	Heterogeneity		
					X^2	I^2	P-Value
Ethnicity							
Asian	14	2433	<.001	2.20 (1.84–2.63)	14.03	7	.37
Caucasian	3	718	.84	1.07 (.56–2.05)	9.42	79	.009
Tumor type							
Hepatocellular carcinoma	2	501	<.001	2.26 (1.51–3.36)	.09	0	.77
Esophageal cancer	4	389	<.001	1.97 (1.36–2.87)	5.40	44	.14
Breast cancer	2	429	.27	1.81 (.62–5.27)	3.90	74	.05
Others	9	1832	.003	2.01 (1.27–3.19)	25.28	68	.001
Sample size							
≤200	10	1064	<.001	208 (1.68–2.58)	10.4	14	.32
> 200	7	2087	<.001	2.14 (1.45–3.14)	19.90	60	.006
HR estimate							
Reported	12	2463	<.001	1.98 (1.41–2.78)	38.81	72	<.001
Survival curve	4	625	<.001	2.19 (1.69–2.83)	1.13	0	.077

Abbreviation: HR: hazard ratios; OS: overall survival; CI: confidence intervals; RFS: recurrence-free survival; DFS: disease-free survival.

Table 4. The link between up-regulated LSD1 and clinical pathological factors analysis.

Clinicopathologic Parameter	Number Studies	OR (95% CI)	P-value	Heterogeneity Test		
				X^2	I^2	P-value
Age (≤ 60 vs > 60)	5	1.03 (.72-1.46)	.88	4.35	8	.360
Gender (male vs female)	10	.70 (.36-1.36)	.29	56.07	84	<.001
Lymph node status (yes vs no)	6	3.37 (1.47-7.75)	.004	12.98	61	.020
Tumor differentiation (poor vs well)	2	1.63 (.18-14.41)	.66	6.95	86	.008
Tumor stage (III–IV vs I–II)	10	2.50 (.97-6.47)	.06	97.37	91	<.001
Vascular invasion (present vs absent)	3	2.48 (.62-9.85)	.20	9.53	79	.009
Tumor grade (T3-T4 vs T1-T2)	7	1.46 (.30-7.12)	.64	134.01	96	<.001

Abbreviation: LSD1: lysine-specific demethylase 1; CI: confidence intervals.

PTM of p53. This is attained via the demethylation of K370me2. Methylation at this site stimulates the relationship of p53 with co-activator 53BP1 and this reaction can be prevented by LSD1.[20] This is achieved when the SNAG domain of Snail which resembles histone H3 tail structurally, employs LSD1 to the epithelial gene promoters leading to the formation of the Snail-LSD1-CoREST complex which later demethylates H3K4me2. [47] MYCN is linked with poor prognosis in neuroblastoma. This shows that up-regulated LSD1 is linked with lower N-Myc downstream-regulated gene 1 (NDRG1) expression and poor prognosis, since there is a relation with the co-localization of LSD1 and MYCN at the promoter of a key suppressor of metastasis, NDRG1, inhibiting its expression.[48] Carnesecchi et al[49] stated that to suppress mesenchymal markers and also decrease tumor invasiveness, there is the need to abrogate SNAG-LSD1 interaction. Luo et al[50] postulated that males absent on the first (MOF) expression is linked with propitious prognosis in cancer since enhancing change to a mesenchymal phenotype is opposed by acetylation of LSD1 MOF.

Is There Any Different Expression Level of LSD1 in Different Tumors?

The expression level of LSD1 in cancer cells is highly significant in cancer development and treatments and it is imperative to know the different levels of LSD1 expression in several cancer cells. It is known that up-regulated LSD1 can lead to aggressive tumor biology.[48] Wu et al[51] and Zhao et al[42] postulated an up-regulated LSD1 in hepatocellular carcinoma (HCC) in liver tissues. The up-regulated LSD1 is linked with higher cancer stage and higher cancer grade as well as reduced survival time in HCC patients. According to Lv et al,[21] lung cancer cells have over-expressed LSD1. For instance, in small-cell lung cancer (SCLC), LSD1 was up-regulated making it a potential therapeutic target in SCLC.[52] Again, Nair et al[53] stated that the up-regulated LSD1 in non-small-cell lung cancer is linked with poor prognosis and encourages proliferation, migration and invasion of the cancer cell.

In T cell acute lymphoid leukemia (T-ALL), LSD1 has been detected to be up-regulated and also characterized by a rare
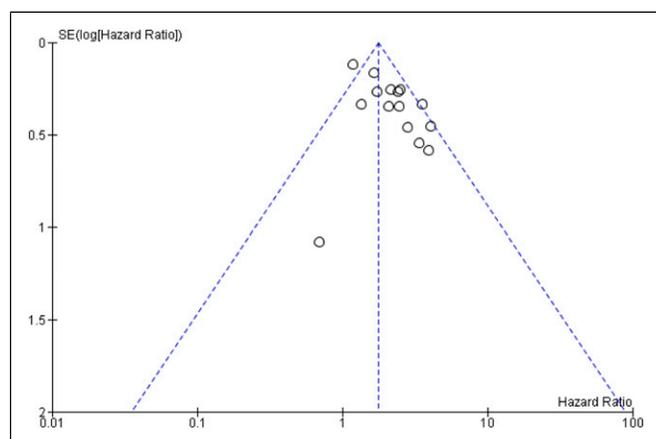
Figure 5. Funnel plot of publication bias on the relationship between lysine-specific demethylase 1 up-regulation and overall survival.

Notch signaling and T-cell progenitor malignancy, initiating from mutations in the NOTCH1 gene.[54]

Lysine-specific demethylase 1 has been considered to be up-regulated in ovarian cancer.[36,55] High levels of LSD1 have been also found in pancreatic cancer cells compared to normal cells and sustain the growth of cancer cells.[56] It has been proven that LSD1 is up-regulated in cutaneous squamous cell carcinoma (cSCC).[57] Kahl et al[58] stated that there is a high level of LSD1 and nuclear FHL2 in prostate cancer and this finding was confirmed by Sehrawat et al[59] who revealed that, despite the independence of its demethylase function, LSD1 enhances the survival of castration-resistant prostate cancer cells. The up-regulated LSD1 which is accompanied by a decrease in E-cadherin expression can be used as a prognostic marker for prostate cancer progression and metastasis.[60] The improved expression of VEGF-A was revealed to be linked with up-regulated LSD1.[61] According to Hayami et al,[18] in human bladder carcinomas, LSD1 expression levels are enhanced specifically in tumors of low grade (G1). Lysine-specific demethylase 1 has been proven to be up-regulated in glioblastoma and encourages the growth of glioblastoma cells.[62]

Sehrawat et al[59] and Maiques-Diaz et al[63] postulated that LSD1 is significantly up-regulated in less differentiated subtypes of acute myeloid leukemia (AML) and the over-expression has been proven to be vital for the growth and maintenance of AML. Medulloblastoma which is closely linked to neuroblastoma has also been revealed to have up-regulated LSD1.[64] LSD1 was up-regulated in esophageal squamous cell carcinoma (ESCC)[65] and demonstrated that inhibiting both LSD1 and Notch pathway with FLI-06, exerts antitumor activity on ESCC. When compared to normal LSD1 levels in oral tissues, LSD1 expression is up-regulated in oral cancers.[24] The inhibition of LSD1 improves E2F1 signaling activities and its overexpression results in poor clinical outcomes.[66] According to Bradley et al,[67] when exposed to the cancer-causing agents, LSD1 will be up-regulated and may encourage the manifestation of primary stage breast cancer. Up-regulated LSD1 encourages ductal carcinomas in situ (DCIS) to progress into invasive ductal carcinoma,[68] and also hastens development, proliferation, and metastasis of breast tumor cell.[69] Again, Serce et al[69] found that, in high-grade DCIS, LSD1's expression was considerably enhanced compared to that in low-grade DCIS. The improved expression of LSD1 is also detected in the colon and colorectal tumors.[45]

On the contrary, a study by Urbanucci et al[70] and Suikki et al[71] described a little to no up-regulated LSD1 in prostate cancer cells. Again, Harris et al[72] stated that about 60% of AML cases reported have over-expressed LSD1, indicating that not all AML cases have shown LSD1 over-expression. Over-expression of LSD1 was detected in poorly differentiated neuroblastoma cells, and downregulation of LSD1 was found in differentiated neuroblastoma cells.[73] Lim et al discovered up-regulated LSD1 in ER-negative breast cancer tissues. However, Wang et al reported that, in human breast cancer tissues, LSD1 expression levels are decreased and that the level is adversely associated with that of TGF-β1 [67]. Zheng et al[74] confirm the decrease in LSD1 expression levels in breast cancer tissues which are adversely linked with that of TGF-β1. The controversy on expression levels of LSD1 on ER-positive breast cancer and ER-negative breast cancer cells raises the question as to whether LSD1 can be considered as an effective anticancer therapeutic target in breast cancers. From this review, we have established that the expression levels of LSD1 in different tumor cells ranging from solid tumors to AML are different. However, the over-expressed LSD1 level establishes LSD1 as a favorable epigenetic target for the treatment of different tumors.

Lysine-Specific Demethylase 1 Inhibition and Cancer Cell Migration

Up-regulated LSD1 stimulates cancer cell migration.[75,76] A study by Shao et al[77] shows that epidermal growth factor (EGF) signaling up-regulates LSD1 levels in SKOV3 and HO8910 ovarian tumor cells up-regulating LSD1 and EGF receptor. Li et al[75] used a TCP inhibitor to examine the role of LSD1 in cell migration by suppressing the demethylase activity of LSD1 in HO8910 cells. The LSD1 inhibition reduced the migration activity of the HO8910 cells in a dose-dependent manner. This shows that LSD1 is vital for cell migration in HO8910 ovarian cancer cells. Cancer cell migration study after LSD1 down-regulation in the lung adenocarcinoma cell line PC9, by the LSD1 inhibitor HCI-2509 and siRNA, established that up-regulated LSD1 stimulates cancer cell migration in lung adenocarcinoma cell line PC9 [76].

Zhang et al[78] postulated that up-regulated LSD1 enhanced cell migration of MKN-45 and HGC-27 cells. However, the

knockdown of LSD1 in MKN-45 and HGC-27 cells reduced cell migration in gastric cancer. Yu et al demonstrated the relationship between LSD1 expression and ESCC in vitro using TCP. In the wound and transwell assays, LSD1 knockdown leads to a sharp decrease in the migration of KYSE450 compared to control shRNA-treated cells.[22] Pharmacological targeting of the actions of LSD1 using LSD1 inhibitors led to a reduction in REST-dependent cell migration in wound healing, given an indication that REST-LSD1 interaction regulates cell migration in medulloblastoma.[79]

However, in luminal breast cancer cells, Hu et al[80] examined wound-healing assay in cultured MCF7 cells with either down-regulated *LSD1* or inhibitor treatment; both cases led to increased cell migration. Therefore, we deduce that in addition to the cancer suppressor role, LSD1 inhibition could play an oncogenic role in breast cancer, particularly in ER⁻ positive luminal breast cancer.

Lysine-Specific Demethylase 1 Inhibitors in Clinical Trials

A lot of compounds targeting LSD1 are grouped into irreversible and reversible inhibitors. Some of these drugs have entered clinical studies for tumor malignancies, including ORY-1001, CC-90011, INCB059872, TCP, GSK-2879552, IMG-7289, and ORY-2001.[5] Thrombocytopenia has been considered the most prevalent treatment-related adverse event with LSD1 inhibitors in clinical studies. The study by Johnston et al[81] attributed this toxicity to megakaryocytic stem cells.

CC-90011. The CC-90011 inhibitor is the only known reversible LSD1 inhibitor currently being tested in a phase I trial in solid tumors and non-lymphomas Hodgkin's (R/R) (NCT02875223).[82] The study included 50 patients, with solid tumors being 49, one having non-lymphomas Hodgkin's (R/R), and 26 having neuroendocrine neoplasms (NENs). The most common treatment-related AEs were thrombocytopenia and neutropenia, which affected 16 and 8% of the patients, respectively. Thrombocytopenia occurred in 8% of patients due to high dosages. 40% of the patients had serious AEs, with 6% of them being related to the treatment. Peak plasma concentrations occurred 2 to 4 hours after the treatment, with a mean terminal half-life of 60 hours; the exposure was dose-proportional. In response to CC-90011, PD analysis revealed a decrease in CgA and MMD, which corresponded to clinical benefit. One patient had a complete response (CR), while the other 22 had stable disease (SD). SD 4 months was observed in seven patients, five of whom had bronchial NEN and two of whom had prostate NEN.[82]

ORY-1001. Phase II of a clinical trial evaluated ORY-1001 in aged AML patients (ISIN Code: ES0167733015, ORY)[83] and SCLC patients (ISIN Code: ES0167733015, ORY),[84] and phase I/IIa of a clinical trial evaluated ORY-1001 in R/R acute leukemia patients (EudraCT No.: 2018-000482-36).[85] The primary clinical research phase I/IIa with ORY-1001 in R/R acute leukemia patients indicated safety and admirable tolerance of the drug, as well as primary signals of anti-leukemic efficacy, according to Maes et al[85]. The therapy combination treatment of ORY-1001 and azacitidine is proceeding in the phase II investigation of ORY-1001 with AML patients (aged), with promising clinical effectiveness evidence. This study includes 8 patients, 6 of whom have achieved objective responses (OR): complete remissions with incomplete hematologic recovery (CRi) in 3 patients, complete remissions in 2 patients, and 1 partial remission patient. The average monitored period for the evaluable patients was 20 weeks, with an average time to response of 32 days for those who responded. Two out of every 5 patients who received more than 3 cycles of treatment became transfusion independent. Looking at the 27% previous response rates in this population when treated with azacitidine alone,[83] the results support a significant synergistic impact from ORY-1001. Based on preclinical investigations, the phase IIa clinical combo study with ORY-1001 has commenced; the drug combination of ORY-1001 with platinum-etoposide has shown encouraging results. ORY-1001 in combination with platinum-etoposide will be tested for safety, tolerability, dose-finding[84] and effectiveness in patients with SCLC.

Tranylcypromine (TCP) inhibitor. TCP in AML (R/R) (NCT02261779)[86] and TCP in non-APL AML/MDS (NCT02717884)[87] were studied in phase I/II trials. The TCP/ATRA therapy phase I/II clinical trial investigated the safety and efficacy of TCP/ATRA treatment for AML (R/R). The combo trial was estimated in eighteen individuals who did not meet the standards for intense treatment. There was a 20% total response rate, with two complete remissions without hematological recovery and one partial retort. In individuals who did not achieve clinical remission, the TCP/ATRA combination treatment exhibited myeloid differentiation. The median OS was 3.3 months, and the 1-year OS rate was 22%. ATRA-induced differentiation syndrome emerged in one case. The most frequently occurring AE was vertigo and hypotension. There is a link between TCP plasma levels and TCP intracellular concentration. H3K4me1 and H3K4me2 were shown to be elevated in the AML blasts and white blood cells of some of the patients treated with the TCP/ATRA combo. TCP/ATRA medication combo treatment could trigger AML blast differentiation and result in clinical response in heavily pre-treated patients with refractory/relapsed AML with acceptable toxicity.[86] The clinical trial phase I for non-APL AML/MDS is the assessment of MTD of tranylcypromine (TCP) in combination with fixed-dose ATRA and Cytarabine (AraC) to determine the recommended phase II dose (RP2D) in patients with non-APL AML/MDS for whom no standard treatment is available. In phase II clinical investigation, TCP was combined with fixed-dose ATRA and AraC to test TCP effectiveness at the RP2D. It is the first efficacy

evaluation to pave the foundation for additional TCP research.[87] The phase I clinical experiment of TCP and ATRA on non-APL and AML cells was carried out in response to a paper published in Nature Medicine, which validated their hypothesis that non-APL and AML cells can be re-sensitized to ATRA when paired with LSD1 agents.

IMG-7289 inhibitor. In essential thrombocythemia (NCT04081220)[88] and myelofibrosis (NCT03136185),[89] a single inhibitor IMG 7289 was studied in a phase IIb trial. The single inhibitor/ double inhibitor IMG-7289 in AML and myelodysplastic syndrome (NCT03136185) was evaluated in a phase I/IIa trial.[90] The phase I manifold rising dose quota of the trial evaluating IMG-7289 as a single inhibitor for AML and myelodysplastic syndrome was wonderfully completed. The IMG-7289/ATRA combo treatment regimen was evaluated for prolonged dosing periods in the phase IIa development arm of the study. The final IIa expansion cohort is still being treated.[90] The data establishes the prospects of IMG-7289 as a single inhibitor in intermediate-2 and high-risk myelofibrosis patients who are intolerant to Janus Kinase (JAK) inhibitors in the case of myelofibrosis. Phase II trials for IMG-7289 are now underway. "Spleen volume reduction, reduction in total symptom scores, and improvement in circulating inflammatory cytokines, anemia, bone marrow fibrosis, and blast count" are among the clinical endpoints.[89] The phase II trial looks at how well IMG-7289 works in the treatment of essential thrombocythemia, just as it did with essential thrombocythemia. IMG-7289 is crucial because it stops LSD1 from acting. The formation of aberrant cells is linked to upregulated LSD1 in essential thrombocythemia patients. In patients with essential thrombocythemia, IMG-7289 reduces aberrant red cell and platelet counts. IMG-7289 has been shown to reduce the size of the spleen and other inflammatory indicators, which are thought to induce symptoms in these disorders.[89]

GSK2879552 inhibitor. GSK2879552 was in phase I clinical trials as an LSD1 inhibitor for AML (R/R) (NCT02177812) and SCLC (NCT02034123) malignancies). Twenty-nine patients were assigned to this trial for the single inhibitor GSK2879552 in SCLC (R/R) malignancy. The research was completed by 22 patients, with 7 people withdrawing due to adverse events (AEs). At least 1 treatment-related adverse event was experienced by 83% of the participants. Thrombocytopenia was the most prevalent treatment-related adverse event, affecting 41% of participants. Nine patients reported 12 serious adverse events (SAEs), six of which were related to treatment, with encephalopathy (four SAEs) being the most common. The investigation found three deaths, one of which was associated with major adverse events. Quick absorption, slow elimination and a dose-proportional rise in exposure were all characteristics of PK.[91] The orally administered GSK2879552, alone or in combo with ATRA, was used to evaluate the recommended phase II dose (RP2D) and regimen for the orally administered GSK2879552, alone or in combination with ATRA, in patients with relapsed/refractory AML malignancy. The trial was split into two halves. Stage 1 used the dose-escalation approach to determine the maximum tolerated dosage (MTD) and/or RP2D. Stage 2 will investigate the safety, tolerability and clinical activity of GSK2879552 at the RP2D in people with AML, either alone or in combination with ATRA. The phase 2 trial, however, did not take place because the phase I study was stopped early.[92]

Discussion

LSD1 is implicated in various solid tumors and its up-regulation is linked with poor prognosis.[21] Up-regulation of LSD1 has also been observed in many hematologic diseases including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and myelodysplastic syndrome (MDS).[39] It is known that up-regulated LSD1 can lead to aggressive tumor biology.[45] Currently, the correlation between LSD1 up-regulation and patients' survival has been discovered in numerous works[33,35-39,93] due to the vital role of LSD1 in tumorigenesis. The prognostic value of up-regulated LSD1 remained controversial. A study by Zhu et al[17] established that up-regulated LSD1 forecasts unfavorable OS in clear cell renal cell carcinomas (ccRCC) patients. Again, Kim et al[40] showed that up-regulated LSD1 protein is significantly linked with decreased rates of OS in hepatocellular carcinoma patients. A report from Lin et al[38] and Yuan et al[24] demonstrated the same. However, opposite outcomes were also detected in other works.[25] To resolve the prognostic significance of up-regulated LSD1, a meta-analysis was needed to explore the issue. According to Timulak,[94] meta-analysis is a suitable instrument to perceive the effects that may be missed by singular studies.

Our work pooled the survival data of 3151 tumor patients from 17 pieces of research and detected that LSD1 up-regulation was linked with poor OS (HR =2.08, 95% *CI*: 1.66-2.61, $P < .01$) with a pooled significant heterogeneity (I^2=53%, P=.008) and RFS (HR =3.09, 95% *CI*: 1.81–5.26, $P < .01$) with no significant heterogeneity ($I^2 = 0\%$, P=.074) in tumor patients. However, LSD1 up-regulation was not linked to DFS (HR = 1.49, 95% *CI*: .83–2.69, P=.18) but showed a significant high pooled heterogeneity ($I^2 = 74\%$, P = .004). This work is in agreement with the study by Wu et al,[26] who establish that LSD1 up-regulation was linked with poor OS in tumor patients (HR = 1.80, 95% *CI*: 1.39–2.34, P = .000).

These suggest that detected LSD1 up-regulation in some tumor cells could be a prognostic factor. The subgroup examination by tumor types was conducted and the results showed that LSD1 up-regulation was significantly linked with poor outcomes in patients with esophageal tumors (HR= 1.97, 95% *CI*: 1.36–2.87, $P < .01$) and hepatocellular carcinoma (HR = 2.26, 95% *CI*: 1.51–3.36, $P < .01$) tumors. Again, LSD1 was proven to be linked with tumors such as cervical cancer, colon cancer, tongue cancer and non-small-cell lung

cancer. Nonetheless, LSD1 was not linked with poor outcomes in breast cancer patients. Thus, LSD1 could serve as a novel prognostic biomarker for esophageal tumors and hepatocellular carcinoma.

The subcategory examination by ethnicity shows that LSD1 up-regulation was significantly linked with poor outcomes in Asian patients (HR = 2.20, 95% *CI*: 1.54–2.63, *P* < .001). However, LSD1 up-regulation was not linked with poor outcomes in Caucasian patients (HR = 1.07, 95% *CI*: .56–2.05, P=.84). The cause for this discrepancy may be that the number of studies in the subcategories examination was small. Again, subgroup examination for studies that estimated the HR and sample size showed that LSD1 up-regulation was significantly linked with poor outcomes in tumor patients. For the clinical-pathological factor, our results showed that up-regulated LSD1 was significantly linked with lymph node status. However, there was no significant link between up-regulated LSD1 and age, genders, tumor differentiation, tumor stage, vascular invasion, and tumor grade.

Limitation of the Study

There were a lot of limitations in our systematic review and meta-analysis that should be known. First, most of the articles focused on Asian patients and only 3 were carried out among Caucasian patients. Thus, it is problematic to come out with a well-founded deduction on the prognostic value of LSD1 for Caucasian patients. Second, the description of LSD1 up-regulation was not the same across studies; thus, it was difficult to outline LSD1 up-regulation in numerous tumors. This seems to flag the dependability of our study. Also, trials of the outsized number of cases for each definite tumor that is well-designed should be done soon to authenticate the association between LSD1 up-regulation and prognosis of patients with tumors. Third, some of the HRs with their 95% *CIs* were estimated from the survival curves. The estimated HRs from the survival curves could be less dependable than HRs with 95% *CIs* that were directly hauled out from the studies. Lastly, the technique for discovering LSD1 up-regulation in the included studies was immunohistochemistry. However, it was hard to track the constant observing standards wholly for the staining technique; the diverse tissues limit value and antibody concentration.

Conclusion

Despite the limitations in this work, our meta-analysis established that the up-regulation of LSD1 was substantially correlated with poor outcome tumor patients. The subgroup examination detailed that LSD1 may serve as a new prognostic tumor biomarker to monitor the esophageal tumor and hepatocellular carcinoma development and progression. In the future, a larger scale and standard research should be done to confirm our findings.

Data Availability

The data generated and analyzed could be obtained from the corresponding authors on reasonable request.

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