

REVIEW

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LC3 gene expression as a marker of autophagy in acute myeloid and lymphoblastic leukemia: a systematic review

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Abstract

Background Autophagy intensity decreases in most blood malignancies, promoting cancer cell proliferation. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are two main variants of leukemia. *LC3*, an important autophagy gene, and its protein, MAP1LC3B, precisely predict autophagy initiation and progression. The main objective of this systematic review is to investigate the correlation between changes in the expression of the *LC3* gene in patients with ALL and AML.

Methods We performed a literature search in PubMed, Scopus, and Web of Science database in November 20, 2025, using the keywords and MeSH terms. All searches were restricted to sources in the English language, and we focused on human case-control studies where definitive diagnosis was performed using hematological parameters.

Results Initial identification included 1282 articles. Duplicates were removed, leaving 821 papers for screening. From these, 787 articles were removed for inappropriate titles and abstracts, leaving 34 for further review. Ultimately, 10 papers met the criteria for this systematic review. Five AML investigations demonstrated considerably lower *LC3* gene expression than healthy controls. Downregulation was similar in one research. Upregulation was seen in two investigations. In two papers, ALL patients had considerably lower expression than healthy controls. Upregulation was significant in one study and non-significant in another one.

Conclusion The *LC3* gene appears to be downregulated more consistently in AML, suggesting potential diagnostic or prognostic value. However, findings in ALL are inconsistent, and no definitive conclusion can be drawn. Further high-quality studies are required to clarify the role of *LC3* in acute leukemias.

Highlights

1. The primary aim of this systematic review is to examine the association between alterations in the expression of the *LC3* gene in individuals diagnosed with ALL and AML.
2. We identified a total of 1282 citations and selected 10 articles on human case-control studies. These articles included a total of 247 patients with AML, 125 patients with ALL, and 162 control subjects.



3. In most studies, LC3 expression was clearly downregulated in AML, indicating a potential role of autophagy-related pathways in its pathogenesis. However, findings in ALL were limited and inconsistent, making it difficult to draw definitive conclusions.

Keywords Autophagy, Acute lymphoblastic leukemia, Acute myeloid leukemia, LC3, MAP1LC3B

1 Introduction

Leukemia is recognized as one of the most common cancers among the young population and consistently ranks among the top five most prevalent cancers in children and adolescents. Although global incidence varies across regions, it remains a major contributor to the cancer burden in this age group [1]. Acute lymphoblastic leukemia (ALL), which is derived from immature hematopoietic cells and ultimately leads to bone marrow failure, is the most prevalent type of malignancy in children, whereas acute myeloid leukemia (AML), which emerges when atypical myeloid progenitors build up in the bone marrow and peripheral circulation, is a serious hematologic risk that is typically assessed in adults between 65 and 74 years of age [2–5]. Cellular homeostasis is achieved at the basal level in healthy cells [6, 7]. It is dysregulated in a variety of pathological conditions, including cancer [8, 9]. An essential part of preserving cell homeostasis is cell death, a process that has been conserved throughout evolution. Apoptosis, necrosis, necroptosis, ferroptosis, pyroptosis, NETosis, and autophagy are different types of cell death that altered in most hematological malignancies [10–14]. The development of groundbreaking approaches utilizing the immune system's inherent capabilities to combat malignancies indicates the vital importance of finding targeted therapies [15]. Therefore, a comprehensive understanding of the regulation of cellular processes, including autophagy, is essential for identifying new therapeutic targets in oncology [16]. Autophagy is a cellular degradation process that is extremely conserved and helps maintain cellular homeostasis and cell function by the lysosomal degradation pathway, breaking down damaged organelles and malfunctioning cytoplasm [17]. The disruption of autophagy may have a significant impact on the development and initiation of leukemia [3]. Chaperone-mediated autophagy, microautophagy, and macroautophagy are the three different types of autophagy [18]. During the most well-known autophagy, known as macroautophagy, entire cell regions are encased in double-membrane vesicles or autophagosomes. After these autophagosomes combine with lysosomes to form autophagolysosomes, the proteases contained in the autophagolysosomes decompose the components stored in them [19]. Figure 1 demonstrates that each of these steps is strictly regulated by certain proteins, including microtubule-associated protein 1 light chain 3 β (MAP1LC3B). By means of a posttranslational ubiquitin-like conjugation mechanism, the LC3 is covalently bonded to phosphatidylethanolamine (PE), leading to its preferential localization at the autophagosomal membrane. Autophagosome formation depends on the process by which LC3 transforms from its unconjugated (LC3-I) to PE-conjugated (LC3-II) forms [18]. LC3 is a crucial gene associated with autophagy, and its related protein, MAP1LC3B, is a predictor of the beginning and development of autophagy and a component of the autophagy cascade [20–22].

Generally, autophagy may play a dual role in leukemia, according to studies. It can prevent normal hematopoietic cells from changing into leukemia cells, which is one of its

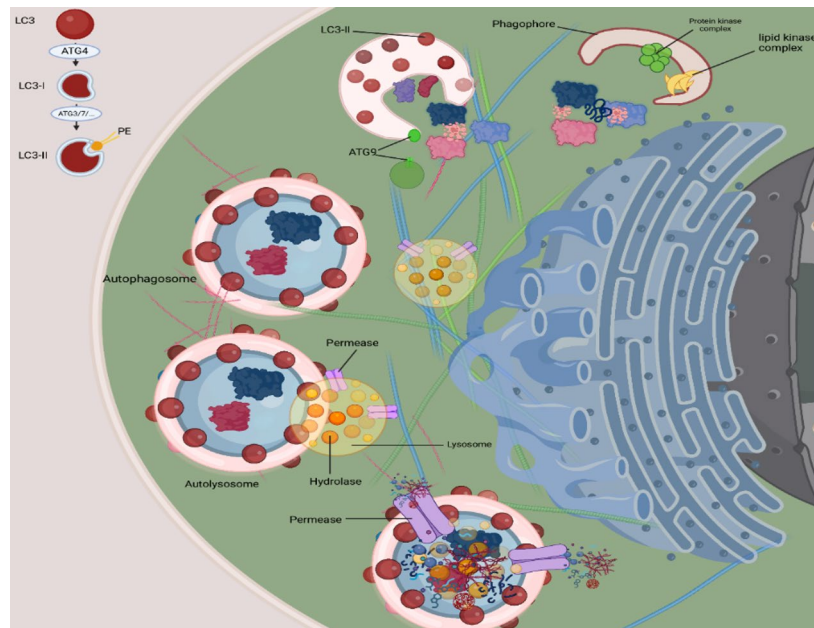


Fig. 1 Schematic role of LC3 in the autophagy process

key anticancer mechanisms. A malfunction in autophagy could be the cause of the onset and progression of leukemia. However, it might also act as a defense mechanism for leukemia cells, assisting them in overcoming harmful environmental stimuli like oxidative stress [23]. Furthermore, the critical autophagy gene *LC3*'s expression level in acute leukemia is still unknown. This gene is more expressed in acute leukemia, according to certain research [3, 24], while less expression is shown in other studies [25–30], so the main aim of this systematic review is to investigate the correlation between changes in the *LC3* gene expression in patients with ALL and AML.

2 Materials and methods

2.1 Systematic search

The systematic search focused on acute leukemia and the autophagy pathway was accomplished in PubMed, Web of Science (WOS), and Scopus databases. We concentrate on *MAP1LC3B*, as an essential marker for developing autophagy. There was no time constraint on the search. The date of the last search was on November 20, 2025. Keywords, abstract, and MeSH terms included "Acute lymphoblastic leukemia" OR "ALL" OR "Precursor Cell Lymphoblastic Leukemia Lymphoma" OR "Lymphoblastic Leukemia" OR "Lymphocytic Leukemia, Acute" OR "Acute Lymphocytic Leukemia" OR "Leukemia, Acute Lymphocytic" OR "Leukemia, Lymphocytic, Acute" OR "Leukemia, Lymphoblastic, Acute" OR "Leukemia, Acute Lymphoblastic" OR "Acute Lymphoblastic Leukemia" OR "Lymphoblastic Lymphoma" OR "Lymphoma, Lymphoblastic" OR "Acute Lymphoid Leukemia" OR "Leukemia, Acute Lymphoid" OR "Lymphoid Leukemia, Acute" OR "Leukemia, Lymphoid, Acute" OR "Leukemia, Lymphoblastic" OR "Lymphoblastic Leukemia, Acute" OR "Leukemia, Lymphocytic, Acute, L1" OR "Lymphocytic Leukemia, L1" OR "L1 Lymphocytic Leukemia" OR "Leukemia, L1 Lymphocytic" OR "Leukemia, Lymphoblastic, Acute, L1" OR "Lymphoblastic Leukemia, Acute, L1" OR "ALL, Childhood" OR "Lymphoblastic Leukemia, Acute, Childhood" OR "Leukemia,

Lymphocytic, Acute, L2" OR "Leukemia, Lymphoblastic, Acute, Philadelphia-Positive" OR "Lymphoblastic Leukemia, Acute, L2" OR "Lymphocytic Leukemia, L2" OR "L2 Lymphocytic Leukemia" OR "Leukemia, L2 Lymphocytic" OR "Lymphoblastic Leukemia, Acute, Adult" OR "Leukemia, Lymphoblastic, Acute, L2" OR "acute myeloblastic leukemia" OR "AML" OR "Leukemia, Nonlymphocytic, Acute" OR "Leukemia, Acute Myeloid" OR "Acute Myelogenous Leukemia" OR "Acute Myelogenous Leukemias" OR "Leukemias, Acute Myelogenous" OR "Myelogenous Leukemias, Acute" OR "Leukemia, Acute Myelogenous" OR "Leukemia, Nonlymphoblastic, Acute" OR "Nonlymphoblastic Leukemia, Acute" OR "Acute Nonlymphoblastic Leukemia" OR "Acute Nonlymphoblastic Leukemias" OR "Myelocytic Leukemia, Acute" OR "Acute Myelocytic Leukemia" OR "Leukemia, Myelogenous, Acute" OR "ANLL" OR "Acute Nonlymphocytic Leukemia" OR "Myeloid Leukemia, Acute" OR "Acute Myeloid Leukemia" OR "Acute Myeloid Leukemia without Maturation" OR "Acute Myeloid Leukemia with Maturation" AND "LC3" OR "MAP1LC3" OR "microtubule-associated protein 1 light chain 3" OR "autophagy-related protein LC3" OR "LC3A" OR "LC3B" OR "LC3C" OR "LC3IIB" OR "autophagy marker light chain 3B" OR "MAP1A LC 3B" OR "MAP1B LC3B" OR "MAP1 LC3B". Furthermore, we collected the citations from pertinent reviews and the literature that was incorporated.

2.2 Eligibility criteria and data collection

Only English-language journal papers were considered in this systematic review, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed during the review [31]. Our study was registered in PROSPERO, with the registration code of CRD42024579408. Excluded items were review studies, manuscripts not published, studies investigating alternative cell death pathways or focusing on unlike autophagy indicators (except *MAP1LC3B*), and studies with any interventions. Moreover, we focused on human case-control studies where definitive diagnosis was performed using hematological parameters. As a result, in vitro and animal studies were excluded. In the event that there was a disagreement between the two reviewers on an article's eligibility, a third expert reviewer decided whether or not to include it.

Two reviewers independently collected data as follows: (i) Author's name, (ii) Year of publication, (iii) Country of study, (iv) Malignancy type, (v) Sample size, (vi) Specimen type, (vii) Gene expression method, (viii) Expression level of *LC3*, and (IX) final conclusion.

2.3 Quality assessment

Quality assessment was measured using the Newcastle–Ottawa Scale (NOS) [32]. The NOS total scores varied from 0 to 9, with scores of 1–3, 4–6, and 7–9 categorized as low-, moderate-, and high-quality studies, respectively. Two reviewers independently carried out the assessment.

3 Results

3.1 Study collection and characteristics

Initially, 1282 articles were identified. After removing duplicates, 821 papers remained and underwent screening. Among these, 787 articles were excluded due to unrelated titles and abstracts, leaving 34 articles for further evaluation. Ultimately, 10 papers met

the criteria for inclusion in this systematic review. The PRISMA flow chart is shown in Fig. 2.

3.2 Characteristics and quality assessment of the studies

Six articles focused on AML patients, two examined ALL patients, and two investigated both malignancies, as shown in Table 1. The included studies incorporated 372 cases, from which 247 were AML patients and 125 were ALL. These studies were published between 2015 and 2025. Five of them were conducted in Iran, two in China, and two in Egypt. The United Kingdom also had one study. The specimen type used for RNA extraction was peripheral blood in four studies, bone marrow in four studies, and in two studies, both of which were assessed. The expression of *LC3* in acute leukemia specimens was evaluated by the quantitative real-time polymerase chain reaction (qRT-PCR) method in all included studies. The methodological scores of the NOS evaluation for each included study are presented in Table 1. The scores of all of the included studies were ≥ 6 points, and the average score was 8.3, indicating their acceptable quality.

3.3 *LC3* gene expression results

The results showed that in five studies involving AML patients, *LC3* gene expression was significantly reduced compared to the non-cancerous control group [25, 28–30, 33]. Also, in one study, the downregulation was not significantly different between the case and control groups [27]. In addition, in two studies, the upregulation of the *LC3* gene was observed, while in one of these studies, the elevation of *LC3* was not significant [3, 24]. The results for ALL patients revealed that *LC3* gene expression was significantly reduced compared to the healthy control group in two studies [25, 26]. Also, a significant upregulation of *LC3* was seen in one study compared to the control group [34]; in another study, although an upregulation of the *LC3* gene was observed, it was not significant when compared to the control group [24].

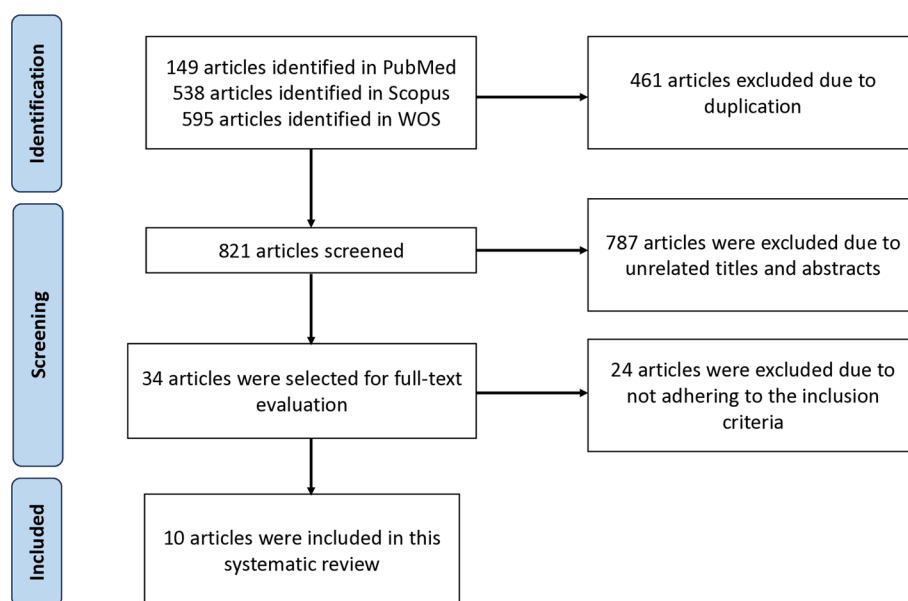


Fig. 2 PRISMA flow chart

Table 1 Characteristics and quality assessment of the included studies

First author	Year	Country	AML/ALL	Sample size	Specimen type	Gene expression method	Expression level of LC3		Final conclusion	NOS score
							Case group	Control group		
Hossein Ayatollahi	2022	Iran	ALL	Case:20 Control: 9	Bone marrow\ peripheral blood	qRT-PCR	1.16±0.39	0.95 ±0.125	upregulated in patients but not significant	9
Radwan	2016	Egypt	ALL	Case: 25 Control: 10	Peripheral blood	qRT-PCR	0.62±0.06	1.01 ±0.11	Significantly downregulated in patients	9
Hayatmanesh	2021	Iran	ALL	Case: 30 Control: 11	Peripheral blood	qRT-PCR	0.15±0.125	0.2 ±0.11	Significantly downregulated in patients	9
Refaai	2025	Egypt	ALL	Case: 50 Control: 50	Peripheral blood	qRT-PCR	0.46±4.74	0.00±1	Significantly upregulated in patients	9
Tandel	2022	Iran	AML	Case: 39 Control: 15	Peripheral blood	qRT-PCR	0.017 ±0.0015	0.0025 ±0.001	Significantly upregulated in patients	9
Huinan Jiang	2019	China	AML	Case: 11 Control: 16	Bone marrow	qRT-PCR	Downregulated but not significantly different		Downregulated in patients but not significant	8
Mohamadreza Mohamadimaram	2019	Iran	AML	Case: 55 Control: 17	Bone marrow\ peripheral blood	qRT-PCR	0.37 ±0.79	0.50 ±0.34	Significantly downregulated in patients	9
Hossein Ayatollahi	2022	Iran	AML	Case: 24 Control: 9	Bone marrow\ peripheral blood	qRT-PCR	2.25±2.25	0.95 ±0.125	Significantly upregulated in patients	9
Radwan	2016	Egypt	AML	Case: 30 Control: 10	Peripheral blood	qRT-PCR	0.60±0.10	1.01 ±0.11	Significantly downregulated in patients	9
P.Q. LIANG	2018	China	AML	Case: 20 Control: 10	Bone marrow	qRT-PCR	Downregulated in patients		Significantly downregulated in patients	8
AS Watson	2015	UK	AML	Case: 8 Control: 4	Bone marrow	qRT-PCR	Downregulated in patients		Significantly downregulated in patients	7
Vahid Amiri	2024	Iran	AML	Case: 60 Control: 20	Bone marrow	qRT-PCR	Downregulated in patients		Significantly downregulated in patients	6

4 Discussion

Autophagy, a remarkably preserved mechanism of programmed cell death, is pivotal in immune reactions, cellular energy processes, programmed cell death, and apoptosis [35]. In certain situations, such as stress, autophagy can break down proteins and impaired organelles within lysosomes through various pathways, supplying energy essential for cellular survival [36]. This pathway involves multiple stages, such as induction, autophagosome nucleation, elongation and maturation, and finally, lysosomal fusion and degradation [37]. For the induction phase, FIP200 protein is important in arranging the ULK complex with the accompaniment of ATG13 and ATG101. Autophagosome nucleation can be triggered by stimulation of protein kinase and lipid kinase complexes [38]. During the vesicle elongation and maturation stage, LC3-PE conjugation is facilitated by ATG7, ATG10, and ATG3. ATG4 processes LC3 into LC3I, which is subsequently transformed into LC3II. LC3II then localizes to the autophagosome membrane, serving as a marker for the autophagy pathway [39, 40]. This lipidation leads to the recruitment of ubiquitinated p62, which is attached to cargo molecules destined for degradation [41]. In the final stage, autophagosomes merge with lysosomes to create autolysosomes, which selectively degrade autophagic cargoes [42].

Remarkably, autophagy exhibits a bipartite influence within oncogenesis. During the nascent stages, it predominantly acts as a suppressor of carcinogenic cell proliferation. On the other hand, in the latter stages, it provides resilience against stressors such as anoxia and nutrient scarcity, thereby facilitating drug resistance and contributing to oncogenic progression [43]. Autophagy in hematological malignancies is not exempt from this, and that dual function has been reported in several studies [44, 45]. Modulating autophagy may be an effective strategy for treating various AML subtypes and overcoming drug resistance [46]. Thus, studying the alteration of *LC3* gene expression in acute leukemia patients can clarify this pathway more than previously understood. To the best of our knowledge, this is the first systematic review to assess *LC3* gene expression in patients with AML and ALL although only ten studies have reached the inclusion criteria for this systematic review.

In AML patients, the downregulation of *LC3* gene expression was more predominant. However, in two studies, upregulation of that gene expression was observed. This discrepancy might be due to differences in AML types or the degree of progressive cancer at the time of definitive diagnosis in the studies included. Regarding ALL patients, the available evidence is more limited, as only four studies have examined *LC3* expression in this group. Among these, two studies reported a significant reduction in *LC3* gene expression compared with healthy controls. Conversely, one study demonstrated a significant upregulation of *LC3*, while another showed a non-significant increase. Given these inconsistent findings and the small number of available studies, no definitive conclusion can be drawn about *LC3* expression patterns in ALL [24, 34, 47, 48]. In addition, it was reported that Arsenic trioxide (As_2O_3) and Doxorubicin induced anti-leukemic effects in primary AML progenitor cells through autophagy mechanisms in vitro [49, 50]. These findings suggest that the loss of autophagy genes might generally promote tumor growth. However, some studies do not fully support this deduction [51]. Consequently, more original studies are needed to validate this assumption.

Triggering cellular autophagy through certain interventions can be a potential mechanism to overcome drug resistance in various cancers, including AML and ALL. Targeting

AML cells with *LncSIK1*, a novel lncRNA, has been reported to reduce the resistance of AML cells to retinoic acid by regulating the autophagy pathway [52]. Future original studies are recommended to stimulate the expression of the *LC3* gene, which is a crucial predictor of autophagy.

These findings cannot be generalized to other cancers. For instance, breast cancer and hepatocellular carcinoma patients with high *LC3* protein expression had worse overall survival [53, 54]. Conversely, there was no correlation between *LC3* protein expression and overall survival in ovarian cancer patients [55]. However, colorectal cancer patients with elevated *LC3* protein expression showed a favorable overall survival [56].

The variability in *LC3* expression reported across studies highlights a considerable level of inter-study heterogeneity, influenced by differences in patient populations, sample sources, and technical approaches. In the included studies, the AML patients' age was significantly higher than that of ALL patients, and the age range and mean of patients and healthy control groups were almost close together. In addition, in almost all of the related studies, it was stated that there was no significant association between the expression of *LC3* and age of the patients. In the included articles related to AML, there were varied FAB/immunophenotypic subtypes, such as AML M3 and AML non-M3, which could be a potential heterogeneity among the studies. However, in Tandel's study, the AML patients were classified into M3 and non-M3, but no significant correlation was identified between the expression of autophagy-related genes and the subtype of patients at diagnosis [3]. Another potential inter-study heterogeneity is the differences in risk stratification among studies, which can influence the baseline activity of the autophagy pathway. For instance, high-risk mutations such as *FLT3*-ITD are associated with higher autophagy via *ATF4* activation in AML [57]. Also, it was reported that *TP53*-mutant AML exhibited higher autophagic flux compared to *TP53* wild-type AML [58]. Moreover, leukemia status (newly diagnosed or relapsed phase) is another major source of variation although most of the studies evaluated the gene expression in de novo patients, and we excluded those with any intervention or treatment for patients before gene expression analysis. In addition, the bone marrow microenvironment is structurally different from peripheral blood, with altered metabolic and stress signaling in the marrow that could affect autophagic regulation [59]. This difference may cause variations in *LC3* expression. However, all of the included studies used *GAPDH* or *beta actin* genes for normalization, but this diversity may affect the reliability of normalization and influence the relative gene expressions. Technical differences also contribute to heterogeneity. Variability in RNA extraction methods, RNA integrity, and the anatomical site of aspiration can alter the RNA quality and influence qPCR results. Finally, differences in qPCR assay efficiency, primer design, and instrumentation introduce additional technical variability.

In this study, we should acknowledge several limitations. Besides *LC3*, other autophagy-related markers, such as *Beclin-1* or *p62*, could also be investigated to clarify the role of autophagy in acute leukemia patients. Additionally, out of the nine included studies, seven were from Asia, one from Egypt, and one from the United Kingdom. The absence of studies from other regions may hinder our ability to establish correlations between changes in the *LC3* gene expression among acute leukemia patients in those areas. Furthermore, we recognize that protein expression results hold greater validity than gene

expression results due to post-translational modification changes [60, 61]. However, the studies included in our systematic review did not provide data on protein expression.

5 Conclusion

In most studies included in this systematic review, downregulation of *LC3*—and consequently the affected autophagy pathway—was consistently observed in patients with AML. However, findings in ALL were markedly inconsistent, with studies reporting both decreased and increased *LC3* expression. Therefore, while *LC3* may have potential diagnostic or prognostic value in AML, current evidence is insufficient to draw definitive conclusions for ALL. Future large-scale, well-designed studies are required to validate these findings and clarify the role of *LC3*, particularly when evaluated alongside additional autophagy-related genes.

Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
MAP1LC3B	Microtubule-associated protein 1 light chain 3β
MeSH	Medical subject headings
PE	Phosphatidylethanolamine
WOS	Web of science
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle-Ottawa scale
qRT-PCR	Quantitative real-time polymerase chain reaction
FIP200	FAK family-interacting protein of 200 kDa
ULK	Unc-51-like kinase 1
ATG13	Autophagy-related protein 13
ATG101	Autophagy-related protein 101
ATG7	Autophagy-related protein 7
ATG10	Autophagy-related protein 10
ATG3	Autophagy-related protein 3
ATG4	Autophagy-related protein 4
lncRNA	Long non-coding RNA

Acknowledgements

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

Author contributions

PM designed the study. FS accessed pertinent literature sources. RK, HT, and AH screened the retrieved literature, extracted data from included studies, and drafted the manuscript. SD and PM revised the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received for this study.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The data supporting our findings in this paper were obtained freely from websites, and no ethical approval or written informed consent for participation was necessary.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 2 November 2025 / Accepted: 27 January 2026

Published online: 31 January 2026

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