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Review Article

DOES MICRORNA-140 PLAY A ROLE IN THE DEVELOPMENT AND PROGRESSION OF OESOPHAGEAL SQUAMOUS CELL CARCINOMA? - A SYSTEMATIC REVIEW.

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ABSTRACT

Background
Oesophageal squamous cell carcinoma (OSCC) is one of the most common and lethal cancers worldwide. Despite advances in treatment, the five-year survival rate for OSCC remains suboptimal. Recent studies reveal that microRNAs (miRNAs) are involved in developing and progressing various types of cancer. Therefore, the modulation of miRNAs could have implications for new OSCC treatments. The purpose of this research was to summarise the published evidence on the impact of miRNA-140 on OSCC development and progression.

Methods
PubMed and Scopus were searched for the relevant literature. Study inclusion criteria were: basic science studies published during 1 June 2014–1 June 2023. Study exclusion criteria were: research without an appropriate analysis, non-English language publications, and grey literature. No study quality assessment tool currently exists for basic science studies, and all studies that met the eligibility criteria were incorporated in the review. The literature search results were analyzed with descriptive statistics (frequencies, percentages) and presented as a narrative synthesis.

Results
Eight papers were included in this review. All included studies were from China, and ECA109 was the most common OSCC cell line used (8 studies, 100%). Findings from studies involving transfection of OSCC cell lines with miRNA-140 mimics suggest that increased levels of miRNA-140 impair OSCC development and progression. Several genes appear to be regulated by miRNA-140 in OSCC development and progression (NFYA, ZEB1 & 2, ErbB4, and NRIP1). Hypoxia reduces miRNA-140 levels, thereby promoting OSCC development and progression. High levels of miRNA-140 were found to confer resistance to platinum-based chemotherapy drugs.

Conclusion
miRNA-140 plays multiple roles in the development and progression of OSCC, including influencing tumorigenesis, apoptosis of tumor cells, genome instability, invasion, metastasis, and chemotherapy resistance.

Recommendation
More research is needed to extend and validate these results, and to develop OSCC therapies aimed at modulating miRNA-140.

Keywords: *Oesophageal cancer, MicroRNA-140, In vitro*
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INTRODUCTION

Oesophageal cancer (OC) is a highly malignant and aggressive cancer of the oesophagus. [1] Commonly diagnosed in middle age, this type of cancer is more prevalent in males than females.[2] OC is classified into two main histological subtypes: squamous cell carcinoma and adenocarcinoma, both named after the cells they originate from. [2] Approximately 90% of all OC cases reported are oesophageal squamous cell carcinoma (OSCC), and 10% are oesophageal adenocarcinoma (OA). [3] The global incidence of OC varies greatly, with the highest incidences seen in east and southeast Asia, followed by the eastern and southern regions of Africa. [4] According to a global database of cancer statistics and information (GLOBOCAN), there were 604 000 new cases of OC and 544 000 deaths associated with this disease reported in 2020,[5] It is ranked the 8th most diagnosed cancer and the 6th leading cause of cancer-related mortality globally.[5]

Risk factors for OSCC include first- and second-hand smoking, excessive alcohol consumption, and, diet.[6] OSCC is common in developing countries, most of the newly diagnosed cases are from the south-central and eastern regions of Asia, and the eastern and southern regions of Africa. [7] Diagnosis of OSCC is made through a combination of imaging modalities such as CT scan, endoscopy, and biopsy. [6] Treatment for OC includes chemotherapy, radiation therapy, and surgery. Even though these treatment options exist, the response rates are only as high as 64% for surgery, 35% for single-drug chemotherapy regimens, and 60% for combination chemotherapy treatments, [8,9] and outcomes depend on the stage of the cancer at diagnosis and the individual characteristics of the patient. With early detection and optimal treatment, five-year survival rates for OSCC can be as high as 70%, but a proportion of patients, especially in developing countries where 80% of OC cases occur and where survival may be as low as 5%, may not have any clinical response to these conventional treatments. This necessitates the development of new treatment modalities for OSCC.[9–11]

Molecular biology has had a tremendous impact on cancer treatment. By better understanding the molecular alterations during carcinogenesis, researchers can develop new therapies and treatments to control tumor growth and development.[12] Molecular biology has allowed us to better understand carcinogenesis and identifying key molecules involved in these processes is critical to developing new strategies for diagnosis and treatment of OSCC. MicroRNAs (miRNAs) are one such molecule. These are small non-coding RNA molecules that regulate gene expression in several different ways. They are found in all eukaryotic cells and are involved in a range of biological processes, including cell differentiation, embryonic development, and disease development.[13]

What is known about miRNAs and cancer?

Several miRNAs have been linked to cancer development and progression.[14] More specifically, several studies have shown that miRNA-140 is linked to tumor growth and invasion in different types of cancers including breast, cervical, and hepatocellular carcinoma (HCC). [15] This miRNA is thought to exert its anticancer effects by targeting the fibroblast growth factor 9 (FGF9) and transforming growth factor-beta (TGF-β) receptor 1, which are involved in tumor growth and metastasis.[16,17]

What is not known about miRNAs and oesophageal cancer?

The role of miRNAs in cancer development and progression is an emerging field of cancer science research. With specific reference to miRNA-140, an earlier review reported on the impact of several miRNAs on oesophageal cancer, but not miRNA-140 itself.[14] Given that more recent evidence suggests that this particular miRNA might be of importance in the context of oesophageal cancer, a summary of existing published information on miRNA-140 and OSCC would have important implications for guiding future studies that explore OSCC treatments based on miRNA-140 modulation.

The purpose of this study was to summarise the published evidence on the impact of miRNA-140 on OSCC development and progression.

METHODS

Review registration and reporting

This systematic review was registered with the Open Science Framework (OSF) (DOI: 10.17605/OSF/IO/RX7UM). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to guide the conduct of this systematic review.

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Literature search

PubMed and Scopus were searched to identify relevant studies. PubMed and Scopus were selected for two reasons: Firstly, these are the most commonly used medical literature databases and are carefully curated to ensure that only reputable journals are indexed. Secondly, the author's institution did not have access to databases such as EMBASE and CINAHL and had to omit these databases from the literature search. The search strategy for both databases is included in Table 1. The following framework was used to develop the search strategy: P (Population) – OSCC, E (Exposure) – miRNA-140, C (Comparator) – Not applicable, O (Outcome) – Development and progression of OSCC.

Table 1: Search strategy used in the PubMed and Scopus literature searches

Database	Search strategy
PubMed	((miRNA-140 OR miR-140 OR hsa-miRNA-140 OR microRNA-140) AND ("esophageal cancer" OR "esophageal neoplasm*" OR "esophageal carcinoma" OR "esophageal tum*" OR "oesophageal cancer" OR "oesophageal neoplasm*" OR "oesophageal carcinoma" OR "oesophageal tum*" OR "oesophageal malignancy" OR "esophageal squamous cell carcinoma" OR "esophageal adenocarcinoma" OR "oesophageal squamous cell carcinoma" OR "oesophageal adenocarcinoma" AND "differentiation" OR "invasion" OR "tumorigenesis" OR "proliferation" OR "oncogenesis" OR "cancer development" OR "carcinogenesis"))
Scopus	((TITLE-ABS-KEY (miR-140) OR TITLE-ABS-KEY (microRNA-140) OR TITLE-ABS-KEY (hsa-miRNA-140)) AND (TITLE-ABS-KEY ("oesophageal cancer") OR TITLE-ABS-KEY ("oesophageal neoplasms") OR TITLE-ABS-KEY ("oesophageal carcinoma") OR TITLE-ABS-KEY ("oesophageal tumour") OR TITLE-ABS-KEY ("oesophageal malignancy") OR TITLE-ABS-KEY ("esophageal squamous cell carcinoma") OR TITLE-ABS-KEY ("oesophageal squamous cell carcinoma") OR TITLE-ABS-KEY ("oesophageal adenocarcinoma") OR TITLE-ABS-KEY ("esophageal adenocarcinoma") AND TITLE-ABS-KEY ("differentiation") OR TITLE-ABS-KEY ("invasion") OR TITLE-ABS-KEY ("tumorigenesis") OR TITLE-ABS-KEY ("proliferation") OR TITLE-ABS-KEY ("oncogenesis") OR TITLE-ABS-KEY ("cancer development") OR TITLE-ABS-KEY ("carcinogenesis")))

Additional search limits: 1 June 2014 – 1 June 2023

Study screening and selection

Two reviewers independently screened the search results from the two literature databases. The results from the two databases were downloaded as a Microsoft Excel spreadsheet to simplify the screening of the manuscript titles and abstracts. Disagreements between the two reviewers were resolved by a third reviewer. The eligibility criteria used to screen the manuscripts obtained from PubMed and Scopus searches are outlined in Table 2.

Table 2: The inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Basic science studies using cell lines to assess the role of miRNA-140 in OSCC development and progression. Studies published between 1 June 2014 and 1 June 2023	Studies that do not present the findings of an appropriate statistical analysis to investigate the role played by miRNA-140 in OSCC development and progression. Studies not published in the English language. Grey literature (non-peer-reviewed materials)

Data collection

After potentially eligible papers were identified, the full-text articles were reviewed by two reviewers. Relevant information such as study characteristics, cell line information, intervention details, and results of the in vitro experiments related to the impact of miRNA-140 on OSCC were extracted from each eligible manuscript. If the two

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reviewers disagreed, the disagreements were discussed to reach an agreement by clarifying discrepancies or uncertainties. If there was no resolution after the fact, a third reviewer was consulted. Since there was no standard quality assessment tool/EQUATOR tool for basic science studies that existed at the time that this review was conducted, all eligible studies were included in the data analysis and narrative synthesis. The extracted data was entered directly into a Microsoft Excel spreadsheet.

Data analysis

Descriptive statistics (frequencies, percentages) were used to summarize the key characteristics of the manuscripts included in this review. No meta-analysis was carried out.

Ethics Committee Approval Information

This research was approved by the Health Research Ethics Committee of Stellenbosch University, South Africa (Project 27991/2023).

RESULTS

The study selection process is shown in Figure 1. The PubMed and Scopus database searches returned 21 potentially eligible papers. After the duplicates were removed and the eligibility criteria were applied, there were 8 papers included in this systematic review.[18–25]

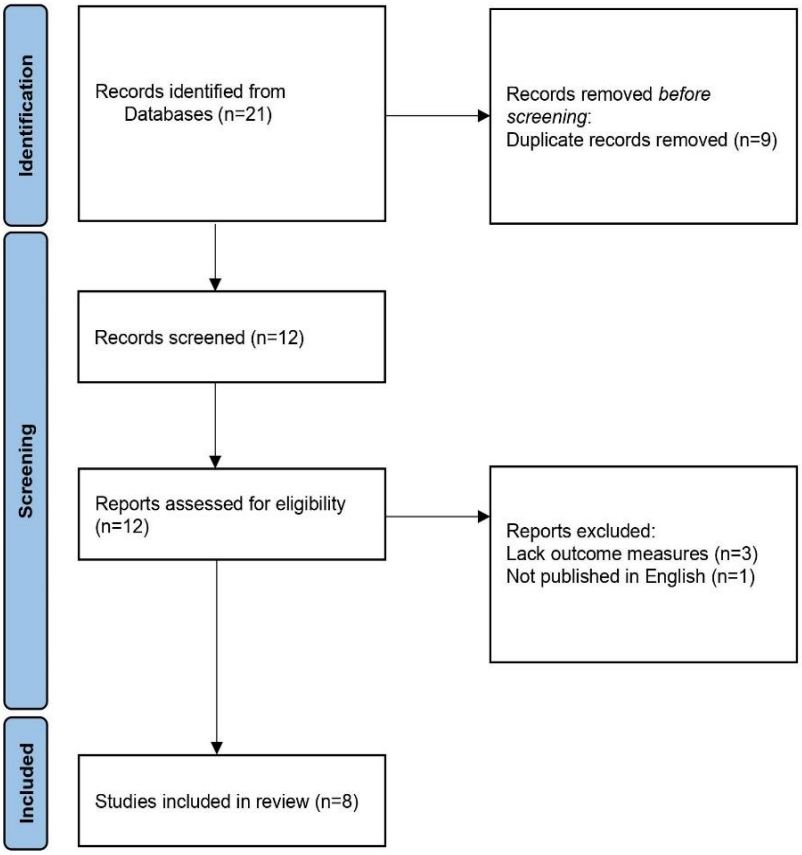

Figure 1: Outline of study selection for this systematic review

The main characteristics of the included studies are summarised in Table 3. All studies included in this systematic review originated from China. All eight studies were experimental. The most common OSCC cell line used in the experiments was ECA 109 (8 studies, 100%), followed by TE-1 (7 studies, 87.5%), and EC9607 (5

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studies, 62.5%). One study (12.5%) used the human leukemia monocyte cell line (THP-1).

Table 3: Main characteristics of the included studies

Author (year)	Country	Cell lines	
		OSCC cell lines	Normal oesophageal epithelial cell lines
Li et al. (2014).[18]	China	ECA109, TE-1	-
Zhao et al. (2014).[19]	China	ECA109, EC9706, TE-1	HET-1A
Zhang et al. (2018).[20]	China	ECA109, ECA9706, KYSE30, KYSE-70, TE-1	HEEC
Chen et al. (2020).[21]	China	ECA109, EC9706, KYSE-30, KYSE-150, TE-1,	HET-1A
Lu et al. (2020).[22]	China	ECA109, TE-1, THP-1*	-
Wang et al. (2021).[23]	China	ECA109, EC9706, KYSE-30, KYSE-41, KYSE-150, SHEE	-
Yang et al. (2021).[24]	China	ECA109, TE-1	HEEC
Song et al. (2022).[25]	China	ECA109, EC9706, KYSE-150, TE-1	SHEE

*Human-derived monocyte-macrophage

Seven studies investigated the impact of miRNA-140 on cell migration and invasive capability using the transwell assay (87.5%). The dual luciferase assay was used to study gene transcription in response to miRNA-140 and the underlying regulatory mechanism for this gene transcription in all 8 studies (100%). The polymerase chain reaction (PCR) was used to measure gene expression levels in four studies (50%). OSCC cell line viability and proliferation were assessed with the MTT assay in 2 studies (25%). All eight studies (100%) used western blotting to measure protein levels, gene expression, and markers of epithelial-to-mesenchymal transition (EMT).

The main findings around miRNA-140 from each study are summarised in Table 4. MiRNA-140 overexpression due to transfection of miRNA-140 into the cell culture and mimic transfections was found to inhibit OSCC cell proliferation, invasion, and migration. More specifically, 6 studies (75%) found that overexpression of miRNA-140 inhibited OSCC cell proliferation, invasion, and migration. The remaining 2 studies did not find a significant effect of miRNA-140 overexpression on OSCC cell proliferation or migration. In one study, high expression of miRNA-140 was shown to confer resistance to oxaliplatin and another showed exposure to hypoxia led to lower levels of miRNA-140 resulting in M2 polarization (promotes cancer cell invasion and proliferation as well as immune suppression). Seven studies (87.5%) found that miRNA-140 influenced the apoptosis of cancer cells, either increasing (6 studies, 75%) or decreasing (1 study, 12.5%) the apoptotic ability of the cells. The included studies identified several genes, RNA molecules, and proteins that interact with miRNA-140. This includes NFYA, MDR1, circ_0087378, circNTRK2, NRIP1, Slug, ErbB4, ZEB1, ZEB2, and SNHG16. Three studies (37.5%) assessed the levels of miRNA-140 in OSCC tumor tissue compared to normal adjacent tissue and found it to be downregulated in tumor tissue and upregulated in normal tissue. Furthermore, three other studies (37.5%) found the expression levels of competing endogenous RNAs to be upregulated in OSCC tumor tissue compared to normal tissue. These results correspond with the results of the *in vitro* studies.

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Table 4: Summary of main findings from included studies

Author (year)	Main Findings
Li *et al.* (2014).[18]	High levels of miR-140 (transfection with miRNA-140 mimic) attenuated OSCC cell invasion whilst low expression of miR-140 promoted OSCC cell invasion. miRNA-140 may regulate OSCC cell invasion via Epithelial-to-mesenchymal transition contributing to tumour metastasis and stage of oesophageal cancer
Zhao *et al.* (2014).[19]	Overexpression of miRNA-140 inhibited the proliferation of OSCC by directly targeting ErbB4 *in vitro*. Increased expression of miRNA-140 was also shown to silence ErbB4 and increase apoptosis of OSCC tumor cells.
Zhang *et al.* (2018).[20]	High levels of MiRNA-140 were shown to inhibit the progression of OSCC by reversing EMT to MET phenotype *in vitro*. Furthermore, SNHG16 functioning as an oncogenic long non-coding RNA may facilitate tumor progression by sequestering miRNA-140-5p, thereby regulating the expression of the target gene ZEB1.
Chen *et al.* (2020).[21]	circNTRK2 functioned as a molecular sponge for miR-140-3p, alleviating its inhibitory effect on NRIP1, and consequently promoting cell proliferation and invasion in OSCC. Overexpression of circNTRK2 attenuated miRNA-140 induced inhibitory effects on OSCC cell malignant phenotypes.
Lu *et al*. (2020).[22]	Hypoxia reduced levels of functional miRNA-140 in OSCC cells through hypoxic exosomal hsa-circ -0048117 acting as a competitive endogenous RNA for miRNA-140 with TLR4. This was shown to possibly activate pathways that promote cellular responses (including polarization of M2 macrophages) promoting invasion and migration of cancer cells
Wang *et al*. (2021).[23]	circ_0087378 serves as a competitive endogenous RNA for miR-140-3p, acting as a sponge for miR-140 and thereby increasing E2F3 expression. This modulation of the miR-140-3p/E2F3 axis ultimately leads to the promotion of tumorigenesis in OSCC.
Yang *et al.,* (2021).[24]	*In vitro* results showed high levels of miRNA-140 inhibited proliferation and invasion in OSCC cell lines by directly targeting ZEB2 through inactivation of the Wnt/b-catenin pathway. Overexpression of ZEB2 reversed the apoptotic effects of miRNA-140.
Song *et al.* (2022).[25]	MiRNA-140 was found to be upregulated in chemotherapy-resistant OSCC cell lines (resistance to the platinum-based therapeutic drug, oxaliplatin) compared to sensitive cell lines. After exposure, miRNA-140 increased cell survival and decreased apoptosis, conferring resistance to oxaliplatin. This resistance effect can be reversed by NFYA expression.

DISCUSSION

This systematic review investigated the role of miRNA-140 in the development and progression of OSCC, and possibly identified genes and pathways that can be targeted to create more effective and safer treatment options. The results showed that miRNA-140 plays multiple roles in the development and progression of OSCC, including influencing tumorigenesis, apoptosis of tumor cells, genome instability, invasion, metastasis, and chemoresistance.[18–25] The implications of these findings are far-reaching, offering insights into OSCC cancer biology and potential future treatment strategies. MiRNA-140 has an important role in the development and progression of OSCC. Several miRNAs have been identified as biomarkers in different carcinomas, but fine-tuning is necessary as the poor overlap is seen in previous studies and no standardized procedure for the preparation and processing of miRNAs exists which can present false results. Prospective studies are therefore needed to evaluate the clinical utility including sensitivity, specificity, and predictive value, particularly in identifying early-stage OSCC and predicting treatment response. MiRNA-140 modulation can be a great complement to conventional treatment, necessitating the development of effective strategies through miRNA-140 mimics or inhibitors, small interfering RNAs (siRNAs), or nanoparticle-based delivery systems. The potential synergies of combining miRNA-140 modulation with, conventional chemotherapy, immunotherapy, or targeted therapies could potentially enhance treatment outcomes.

Expanding research on miRNA-140's molecular mechanisms, particularly in high-incidence regions like Africa is crucial. More prospective studies are needed to validate whether these findings can be replicated in African

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settings to ensure broad applicability. OSCC development and progression involve complex regulatory networks involving miRNAs, genes, pathways, and proteins. Considering the multiple regulatory networks unveiled in the context of miRNA-140 and its involvement in OSCC development and progression, there is a compelling need for future research to embrace a multi-omics approach. Exploring the combined analysis of transcriptomic, proteomic, and genomic data holds significant promise in providing a nuanced understanding of how miRNA-140 interacts within the broader regulatory landscape of OSCC. This comprehensive perspective is paramount for identifying novel therapeutic targets that could form the basis for more effective, precisely targeted treatments in the ongoing pursuit of advancing OSCC research and clinical interventions.

The geographical distribution of studies included in the systematic review was notably unbalanced, as all included studies originated from China. Overall, the majority of OSCC genomic studies are carried out in this region.[26] The African oesophageal cancer corridor, another OSCC hotspot, remains largely underrepresented in OSCC genomic research. [27–29] The lack of research from other regions where OSCC is a public health problem hinders the setting-specific understanding of OSCC aetiology and the development of effective prevention and treatment strategies. There is also the danger that the choice of genes/pathways in Chinese studies might be informed by OSCC genetics that have relevance to Asian populations, which might be very different from that of OSCC in populations from other regions. It is therefore crucial that basic scientists from other regions where OSCC is important be encouraged to conduct their setting-specific research.

MiRNA-140 has been shown to inhibit different cellular processes involved in the development and progression of cancer. In this systematic review, several studies reported on competing endogenous RNAs (ceRNA). CeRNAs play a crucial role in diverse biological processes and the development of neoplasms. The role of ceRNAs in cancer development is well documented in gastrointestinal tumors, breast and endometrial cancer, lymphoma, and leukemia.[30] Moreover, they exhibit promise as diagnostic and prognostic biomarkers as well as therapeutic targets.[31] In this systematic review, some studies found ceRNAs to act as sponges, sequestering miRNA-140, orchestrating its downregulation, and affecting its availability and function. [21–23] Several studies have shown these ceRNAs are not only involved in the development and progression of multiple cancers, but they can also induce immunotherapy and chemotherapy resistance. [30] Comprehending the pivotal role of miRNA-140 within the ceRNA network is crucial for formulating strategies that capitalize on its potential as both a diagnostic marker and a therapeutic target for OSCC, paving the way for advancements in OSCC management.

Hypoxia, a condition influencing multiple cancer hallmarks, [32] is implicated in the progression of multiple types of solid tumors, including OSCC. Within the tumor microenvironment, hypoxia induces the expression of genes, such as angiogenic factors, causing the formation of new blood vessels and facilitating tumor growth.[33] Hypoxic tumor cells are also more resistant to chemotherapy due to the altered tumor microenvironment. [34] One aspect uncovered in this systematic review is the impact of hypoxia on miRNA140 in OSCC. Hypoxia was shown to downregulate miRNA-140 levels *in vitro* via an exosomal circular RNA (circ0048117) acting as a sponge thereby inhibiting miRNA-140s tumor suppressing capabilities. [22] The deregulation of miRNA levels is a common phenomenon in solid tumor microenvironments, influencing both oncogenic and tumor-suppressive miRNAs. [35] In this context, miRNA-140 deregulation emerges as a potential predictive biomarker for diagnostic and therapeutic interventions in OSCC. Diagnostic strategies may involve assessing miRNA-140 levels in patient samples, allowing for early detection or prognostic evaluation. Moreover, understanding the regulatory role of miRNA-140 in OSCC under hypoxic conditions may guide the development of targeted therapeutic interventions aimed at restoring or modulating miRNA-140 levels to impede cancer progression. This is a particularly important consideration when planning new therapeutic interventions that might directly or indirectly impair angiogenesis in the tumor.

Chemotherapy resistance reduces the effectiveness of chemotherapy drugs, leading to chemotherapy treatment failure. It is an important barrier to the effective treatment of OSCC. Several mechanisms have been identified causing resistance, including altered transport of drugs, altered cell signaling pathways, tumor microenvironment, and miRNAs interacting with multi-drug resistance proteins.[36,37] Findings from this systematic review showed that upregulated miRNA-140 induced chemotherapy resistance, specifically affecting platinum-based therapies (oxaliplatin), promoting the progression and development of OSCC. [25] The mechanism through which miRNA-140 induces chemotherapy resistance is still unclear but underscores the clinical relevance of understanding how these molecules are related to treatment responses in patients.[37] At present, it appears that miRNA-140 could serve as a predictive marker of chemotherapy resistance in OSCC patients, thereby allowing oncologists to amend

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treatment in patients with emerging chemotherapy resistance at a much earlier stage.

Studies included in this systematic review reported that miRNA-140 regulated several signaling pathways and genes that are involved in apoptosis, cell proliferation, invasion, and metastasis (via epithelial-to-mesenchymal transition - EMT). [38] These genes include SLUG; ZEB1; ZEB2; NRIP1; E2F3; NFYA; and ErbB2. [18–21,23–25] Several of these pathways and genes have been linked to cancer development and progression. miRNA-140 was shown to influence these pathways either by inhibition or promotion. OSCC exhibits a high mortality rate due to its aggressive nature, prominently driven by metastasis. [39] The late-stage diagnosis is intricately linked to the "silent" progression of OSCC, where symptoms may not manifest until the disease has reached an advanced stage. The process of EMT plays a pivotal role in OSCC metastasis, involving key transcription factors such as ZEB1, ZEB2, and SLUG. Dysregulation of EMT and activation of growth factor pathways contribute to the invasive phenotype. In addressing the high mortality rate in OSCC, efforts to unravel the role of EMT regulation in metastasis are imperative. Further investigation on the role of miRNA-140 as a potential biomarker associated with EMT and metastasis could enhance early detection, while therapeutic strategies targeting the EMT process may offer novel avenues for intervention.

LIMITATIONS

This review was limited to published peer-reviewed articles, which could lead to publication bias where the positive effects of miRNA-140 on OSCC development and progression could be overestimated. There might also be a language bias introduced into this study as the investigators could only read/review papers published in English. The review had a small sample size of 8 articles, all of which were from China. Research priorities for genetic or signaling pathways associated with OSCC in Asian populations may not reflect the situation in other regions of the world where OSCC is a public health problem. The quality of reporting and methods was not assessed since there was no standard/EQUATOR quality assessment tool for basic science studies at the time that this review was performed. A standard quality assessment tool should be developed and adopted to enhance the reproducibility and rigor of future basic science studies. No meta-analysis was done, making it difficult to draw firm conclusions on the overall effect of miRNA-140 on the development and progression of OSCC. The database search was limited to PubMed and Scopus, as these were the only databases that the author's institution had access to. Although the results are encouraging, these findings should be interpreted with some caution.

CONCLUSION

This systematic review summarized the current evidence on the role of miRNA-140 in OSCC development and progression. The findings provide valuable insights into the molecular mechanisms underlying OSCC development and progression, particularly the role miRNA-140 plays in regulating key pathways and genes. Overall, these studies collectively contribute to understanding the complex molecular mechanisms involved in ESCC, highlighting the potential of miRNA140 as a biomarker and therapeutic target for OSCC. Whilst these findings are promising, the translation into clinical applications requires further investigation and validation through more mechanistic and animal model studies and clinical trials. Additionally, studies are needed to identify the optimal strategies for modulating miRNA-140 expression in OSCC patients and to evaluate the efficacy and safety of miRNA-140-based therapies for OSCC.

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LIST OF ABBREVIATIONS

OSCC: Oesophageal squamous cell carcinoma
miRNA: micro-ribonucleic acid
OC: Oesophageal cancer
OA: Oesophageal adenocarcinoma
GLOBOCAN: Global database of cancer statistics and information
HCC: Hepatocellular carcinoma
FGF9: Fibroblast growth factor 9
TGF-*β*: Transforming growth factor-beta
OSF: Open science framework
PRISMA: Preferred reporting items for systematic review and meta-analyses
THP-1: human leukemia monocyte cell line-1
PCR: polymerase chain reaction
EMT: epithelial-to-mesenchymal transition
ceRNA: competing endogenous ribonucleic acid
siRNA: small interfering ribonucleic acid

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

1. JKA conducted the data collection, and analysis, and wrote the first draft of the manuscript.
2. HS conducted a critical review of the draft manuscript and was JKA's research supervisor.
3. YM conducted a critical review of the draft manuscript and was JKA's research supervisor.

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2. YM is an associate professor and cancer epidemiologist at Stellenbosch University, South Africa, and a research associate at the Central University of Technology, South Africa.

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