Review Article

# A Systematic Review of the Efficacy and Safety of Sirolimus (Rapamycin) in the Management of Infantile Hemangioma

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ABSTRACT

**Objective:** The use of rapamycin (sirolimus) in the treatment of infantile hemangioma (IH) is a persistent challenge in dermatology. We aim to systematically review the efficacy and safety of rapamycin for IH treatment. **Methods:** We systematically searched PubMed, Web of Science, and Scopus for relevant English papers up to December 2024. After screening the full texts, eight studies met the inclusion criteria. The quality of the included articles was assessed using the Joanna Briggs Institute checklist. Detailed data about the effectiveness and safety of rapamycin in IH were collected. **Findings:** A total of 8 articles published between 2013 and 2021 were included, with 8 cases. The ages of the participants ranged from 3 weeks to 10 years. The most common dose of rapamycin used in these papers was 0.8 mg/m2 twice daily, with a range of 0.1 mg/m2 to 2 mg/m2 daily. Most patients had a response to rapamycin therapy (five out of eight patients). Two cases reported gastrointestinal adverse effects, whereas one developed severe, fatal hypoglycemia after angiography, which the authors considered the role that rapamycin in causing this complication to be unlikely. **Conclusion:** Rapamycin can be a safe and efficient medication in the treatment of IH. Combination therapy, especially in patients resistant to treatment for IH, is a preferred choice for IH treatment and reduces the side effects of propranolol. It is also preferred for the treatment of lesions in the mucosal areas and near important organs.

**KEYWORDS:** *Efficacy, infantile hemangioma, mechanistic target of rapamycin, rapamycin, safety, sirolimus*

## INTRODUCTION

Infantile hemangioma (IH) is the most common benign vascular tumor in infancy, affecting 4%–5% of infants. It appears as a macule and then generates plaque or a tumor.[1-3] Although the majority of cases improve without intervention, complications arise in 10%–12% of patients, making effective therapeutic strategies essential.[4,5]

IH was traditionally managed with corticosteroids, beta-blockers, laser therapy, and surgery.[1,6,7] Since 2008, propranolol has become the preferred treatment due to its proven efficacy in reducing lesion size and improving cosmetic outcomes.[8,9] Although propranolol has been established as a first-line treatment for IH, incomplete therapeutic responses or recurrences (particularly after treatment discontinuation) have been reported in some cases. Furthermore, contraindications to beta-blockers, including PHACE syndrome with vascular anomalies, and poor tolerance due to adverse effects such as bradycardia, hypotension, and hypokalemia, may limit propranolol's applicability in certain patients.[10,11]

Rapamycin, a macrolide compound, is primarily recognized for its immunosuppressive role in transplant rejection.[12,13] In addition, through mechanistic target of rapamycin (mTOR) pathway inhibition, it has the potential to have antiproliferative, anti-inflammatory, and antiangiogenic effects.[14,15] The topical formulation of rapamycin may minimize systemic adverse effects

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while remaining effective for superficial IH. Notably, some case reports demonstrate synergistic effects when used concomitantly with propranolol for aggressive lesions.[16]

Rapamycin efficacy has been discussed in dermatology for conditions characterized by aberrant cell proliferation and vascular anomalies, including tuberous sclerosis complex, Kaposi's sarcoma, and angiofibroma.[17] Rapamycin has been effective in treating vascular lesions, including venous malformations and lymphatic anomalies, in both laboratory and clinical studies. These results suggest it could serve as a useful therapy for IH by addressing the underlying disease mechanisms.[18]

Despite these encouraging findings, questions remain regarding rapamycin's long-term safety, optimal dosing, administration routes, and treatment duration. Differences in study designs and patient populations further complicate the interpretation of existing evidence.[19,20] To address these issues, this systematic review evaluates rapamycin's effectiveness and safety in treating IH, with a focus on lesion reduction, symptom improvement, treatment strategies, and adverse effects. By synthesizing the current data, in this systematic review, we clarify rapamycin's potential benefits and limitations and provide evidence-based guidance for future clinical use.

## Methods

The research study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[21] and the protocol has been entered in the Open Science Framework (OSF) database with a submission number https://doi.org/100.17605/OSF.IO/8EQ4B. Before starting the study, all authors thoroughly examined the inclusion and exclusion criteria and finalized the keywords for the literature search.

A systematic search of PubMed, Web of Science, and Scopus was performed to identify relevant English-language publications. In total, 507 articles published between 2001 and December 2024 were retrieved: 76 from PubMed, 304 from Scopus, and 127 from Web of Science. Our search term included the following keywords: "Hemangioma" OR "Infant Hemangioma" AND "Sirolimus" OR "Macrolids" OR "Rapamune" OR "Everolimus," OR "Rapamycin." In addition, we reviewed the references of related papers to find any relevant studies that may have been missed. We reviewed the titles and abstracts of the identified articles and applied the inclusion and exclusion criteria to exclude irrelevant studies. Supplementary Table 1 shows the search approach and the number of papers in this systematic review.

This systematic review included original studies on the effect of rapamycin in congenital hemangioma. Reports must meet the following criteria to be considered for inclusion in this systematic review: (1) original studies including retrospective and prospective cohort studies, case series, and case reports; (2) written in English; (3) population-based; and (4) have enough data to determine the effect of rapamycin for IH treatment. Exclusion criteria included reviews, conference abstracts, letters to the editor, *in vitro* studies, animal experiments, and duplicate publications. Articles reporting other types of hemangiomas and vascular tumors other than IH were also excluded from the study.

Two authors (EF and FGh) separately assessed the titles and abstracts of the selected papers. EndNote software (version 9.9; Clarivate Analytics, Philadelphia, PA, USA) was used to remove duplicate studies. To make our final selections, we read the full text of the remaining articles. The authors carried out all processes independently to reduce the risk of bias. Disagreements between the two researchers were resolved by discussion. If disagreements continued, a third author (BA) assessed the study and reached the final decision. The methodological quality of each included paper was assessed separately using a Joanna Briggs Institute checklist. Each article in JBI-based reviews received a score of 3, 2, 1, or 0 based on the responses "Yes," "Unclear," "Not applicable," or "No," respectively. The analysis includes papers having at least 18 scores [Supplementary Table 2].

Data from relevant papers were extracted in the following approach: (1) Study information (author, year of publication, study design), (2) Study participant characteristics (number of patients, gender, and average age); (3) Details of hemangioma, including the site of the lesion, presentations; (4) Rapamycin treatment protocols, including dosage, duration, route of administration, and follow-up time; (5) Efficacy, response to rapamycin, decrease in the size of malformation, drug side effects, and major discoveries.

## Results

### Overview of the studies

In the initial database search, we identified 507 articles across PubMed (76), Scopus (304), and Web of Science (127). After 90 duplicates were removed using EndNote software (V.9), 417 abstracts were further evaluated based on their titles and abstracts, resulting in 26 articles. The remaining articles were assessed for eligibility by considering their full texts. Out of those, 18 did not meet the inclusion criteria. In addition, no eligible studies were found by manually checking the

references of the relevant articles. Ultimately, eight studies published between 2013 and 2021 were included: three case reports,[22-24] 2 were case series,[25,26] and 3 were retrospective cohort studies.[27-29] From each study, one patient was included according to the inclusion criteria. Epidemiologically, two studies were carried out in the USA, two in Canada, and one in Turkey, Korea, England, and Spain [Figure 1].

## Publication characteristics

The included studies had eight patients with IH who were treated with rapamycin. The participants' ages ranged from 3 weeks to 10 years. Among them, five were female, one was male, and the sex of two patients was not specified. Rapamycin was administered orally in five cases, topically in two, and in one case, the route of administration was not reported. Case-specific details, including demographics, characteristics, site of IH, clinical manifestations, treatment details, route of drug administration, follow-up duration, outcomes, and adverse effects, are listed together in Table 1.

## Efficacy of rapamycin for the treatment of infantile hemangioma

Of the patients included in the study, two had IH associated with PHACE syndrome (posterior fossa malformations, hemangioma, arterial anomalies, coarctation of the aorta/cardiac defects, and eye abnormalities), and another had deep neck and mixed IH.[24,26] Half of the patients in this study had rapamycin initiated in the 1st year of life (4/8 patients, 50%), compared to age 1-3 years (3/8 patients, 37.5%), and one of patient more than 3 years. Most patients responded positively to rapamycin therapy (5/8). Three showed a complete or near-complete response. A single-center experience evaluated applied oral doses of rapamycin firstly with the dose of 0.8 mg/m$^2$ every 12 h, then by maintaining of a target serum concentration (5–10 ng/mL) for 16 months. It showed good improvement in radiologic evaluation and no lesion growth was identified.[28] Furthermore, Kaylani *et al*. report the promising use of oral rapamycin in a failed pretreated patient with PHACE syndrome and segmental IHat 14 weeks of age.[22] Rapamycin 0.8 mg/m$^2$, added to propranolol, resulted in a almost complete response and improvementof the lesions in deep neck IH and a mixed IH on her left hand in a 1-month-old infant for 9 months.[24]

Two studies showed a minor or moderate response to rapamycin treatment. In a case series of three patients with segmental facial hemangiomas with late growth and recurrent ulceration, only one with PHACE syndrome received topical rapamycin 1% as an adjunctive therapy after unsuccessful treatment when propranolol was discontinued. The combination therapy helped to gradually taper the dose of propranolol and late growth of the lesions. Rapamycin efficacy in treating this patient is uncertain as she was still taking propranolol and

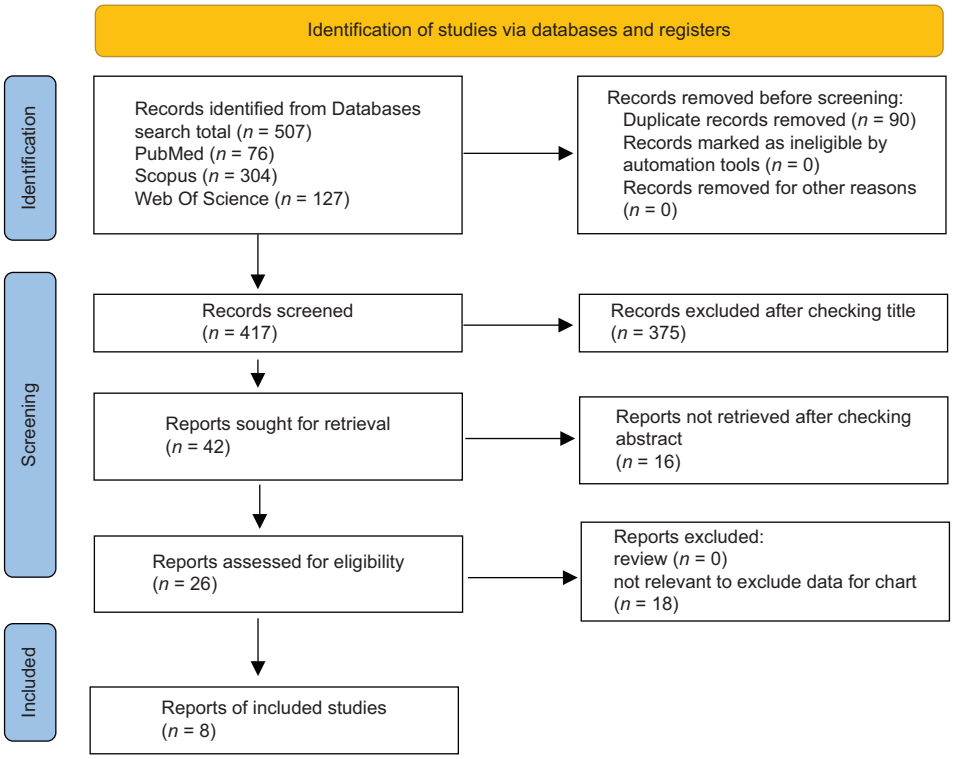


**Figure 1:** Preferred reporting items for systematic reviews and meta-analyses flow diagram

**Table 1: Studies characteristics**

| Author, year | Country | Study design | Total sample, sex | Age | Type of hemangioma | Site of lesion | Clinical manifestations | Rapamycin dosage and prescription | Treatment duration | Route | Other medications | Follow-up duration | Assessment | Outcomes | Adverse effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kaylani, 2013 | England | Case report | 1, female | 3-week-old | IH | Lips | Resultant tenderness and diminished oral intake | 1.5 mg/m$^2$, daily, | Since 14 week of age | Orally | Propranolol prednisone | 14 months | Physical examination | Improving | Neutropenia |
| Kelley, 2017 | USA | Case report | 1, female | 3-year-old | IH | Scalp, chest, abdomen, and back | Hepatos plenomegaly | 0.8 mg/m$^2$, BD | Since 3 years old | Orally | Propranolol prednisone | Till death | Examination and MRI | Moderate improvement | Hypoglycemia |
| Le Sage, 2018 | Canada | Case series | 1 | 2 year | IH | Right forehead | NR | Rapamycin 0.1%, BD | NR | Topical | Topical timolol and propranolol | 16 months | Blood tests, examination | No changes were observed | No complication |
| Tole, 2019 | Canada | Retrospective cohort | 1 | 10 year | IH | Neck, airway | NR | 2.5 mg/m$^2$, daily | At least 6 months | Orally | Corticosteroids, vincristine, nadolol, and laser | 12 months | Imaging, blood tests, and examination | No response | Hypertriglyceridemia |
| Fernandez Faith, 2020 | USA | Case series | 1, female | 7-week-old | Mixed facial segmental IH (PHACE syndrome) | Left lower facial segment | Extended into the oral mucosa and true vocal cords (noted by laryngoscopy), although respiratory symptoms were not present | Topical rapamycin 1%, daily | NR | Topical | Propranolol prednisone | At least 8 years | Examination | Late growth of the lower lip component with ulceration | 5 episodes of ulceration |
| Dávila-Osorio, 2020 | Spain | Case report | 1, female | 1-month-old | Deep neck and mixed IH | Deep neck, mixed IH on her left hand | NR | 0.8 mg/m$^2$, BD | 9 months | Systemic | Propranolol and prednisolone | 8 months | Blood test, examination, MRI, skin biopsy | Near-complete respo nse | An episode of oral aphthae, mild increase in triglyceride levels |
| Oktay, 2021 | Turkey | Case report | 1 | 14 months (10 days-180 months) | IH | Extremities | NR | 1.2 mg–3 mg/m$^2$, daily | 4 year | NR | Propranolol | 10 months (2–132 months) | NR | No positive response to the lesion | Mouth sores, hypertriglyceridemia, frequent infections, or lymphangitis |
| Cho, 2021 | Korea | Retrospective analysis of prospectively collected registry data | 1 | 12 months | IH | Brain, shoulder, chest, arms, legs, anus | NR | Initial: 0.8 mg/m$^2$ Maintenance: 5–10 ng/mL, BD | 16 months | Orally | Propranolol prednisone | 6–12 months | NR | Good response | Stomatitis diarrhea |

IH: Infantile hemangioma; BD: Twice a day, NR: Not reported, MRI: Magnetic resonance imaging, USA: United States of America

topical rapamycin at her last follow-up visit at 8 years of age.[26] In 1 case report of a 3-year-old girl with pulmonary hypertension, hepatic and cutaneous lesions were treated with oral 0.8% rapamycin twice daily at 38 months and showed moderate improvement until her demise due to severe hypoglycemia.[23]

There was no reported improvement in three patients. The clinical course of IH in the extremities showed no positive response to lesions after 1.2 mg to 3 mg/m$^2$/daily rapamycin was administered for 4 years.[29] In a retrospective cohort, one patient had received other therapies before initiating 2.5 mg/m$^2$ rapamycin orally for at least 6 months and showed no significant improvement.[27] One report described no changes after 1 year of application of topical rapamycin 0.1% twice daily.[25]

### Safety of rapamycin for the treatment of infantile hemangioma

The side effects most frequently reported were hypertriglyceridemia and stomatitis, infections, or lymphangitis, and febrile neutropenia in one case,[29] and gastrointestinal symptoms.[28] One case developed severe, fatal hypoglycemia after angiography, yet the authors believed it was unlikely that rapamycin contributed to her demise.[23] In one study, no adverse effect was observed.[25]

Across the included studies, the most commonly reported rapamycin dose was 0.8 mg/m² twice daily, raged from 0.1 mg/m² to 2 mg/m² per day. Before initiating rapamycin therapy, patients had received various treatments, including propranolol, vincristine, prednisolone, nadolol, laser therapy, and topical timolol.

Of the studies reporting follow-up, the mean follow-up duration was 23.57 months. Death was a rare outcome, which occurred in only one patient and was related to severe infection.[23]

## Discussion

To our knowledge, this is the first systematic review evaluating the potential efficacy and safety of rapamycin for the treatment of IH. Eight studies and a total of eight cases were included in the study. The findings suggest that rapamycin may represent a promising therapeutic option for IH. Among the eight cases treated with rapamycin–either orally or topically–five demonstrated a positive response. Importantly, no serious or life-threatening adverse effects related to rapamycin have been reported in these studies.

Significant improvements in IH research have occurred in recent years, understanding the signaling mechanisms involved in IH development.[30] Estrogen, hypoxia, and inflammation appear to play a role in the initial development of IHs, whereas pericytes and mast cells contribute to both their growth and regression. Many factors may play a role in early stage of IH development such as estrogen, hypoxia, and inflammation, whereas pericytes and mast cells are responsible for their growth and regression. Many cellular mechanisms can be impacted by environmental variables. The potential impacts of a particular environmental stimulus (such as inflammation, ischemia, and hypoxia) on the development of IH are typically the focus of current basic research. Some studies emphasize the abnormal activation of environmental factors during embryonic development, whereas others underscore the role of genetic factors in the etiology of IH.[31] Two basic mechanism act in IH pathogenesis are angiogenesis and vasculogenesis by changing in key cellular signaling networks. Ji *et al.* 2014 have examined several molecular pathways involved in IH, including β-adrenergic, PI3K/Protein Kinase B (AKT)/mTOR, vascular endothelial growth factor (VEGF)/VEGF receptor, Notch, Tie2/angiopoietins, HIF-α-mediated, and platelet-derived growth factor (PDGF)/PDGF-receptor-β pathways. These molecular pathways are intriguing from a therapeutic standpoint since blocking them may assist in reversing or preventing hemangioma neovascularization.[32] Treatment options for IH include medication, laser therapy, radiation, and surgery, with the choice depending on the lesion's size, type, and location.[33] Cosmetic treatments are frequently used to prevent psychological consequences.[34] Propranolol is the primary treatment for capillary malformations in clinical practice.[35]

Propranolol may modify neovascularization through various mechanisms such as inhibiting vasculogenesis and catecholamine-induced angiogenesis, disruption of hemodynamic force-induced cell survival, promoting of pericyte-mediated vasoconstriction, and inactivation of the renin-angiotensin system.[30] As explained before, PI3K/AKT/mTOR and Tie2/angiopoietins cellular proliferation pathways are possible mechanisms in the implication of IH, which has been reported in a previous review article.[31,36] Rapamycin is an mTOR, PI3K, and TIE2 pathway inhibitor that reduces protein synthesis for cell proliferation and angiogenesis, potentially inhibiting the formation of vascular tumors.[28,37,38] Figure 2 summarizes the potential mechanisms of rapamycin in the treatment of IH. According to Greenberger *et al*. 2011 results, rapamycin promotes perivascular cell differentiation, reduces the self-renewal potential of IH-derived stem cells, and inhibits angiogenesis.[14] Recent studies have shown that rapamycin can effectively cure vascular malformations and cancers, including IH, without causing significant adverse effects.[39-41] Dávila-Osorio *et al*. 2020 reported that adding rapamycin to propranolol causes the rapid improvement of the lesion while stopping the

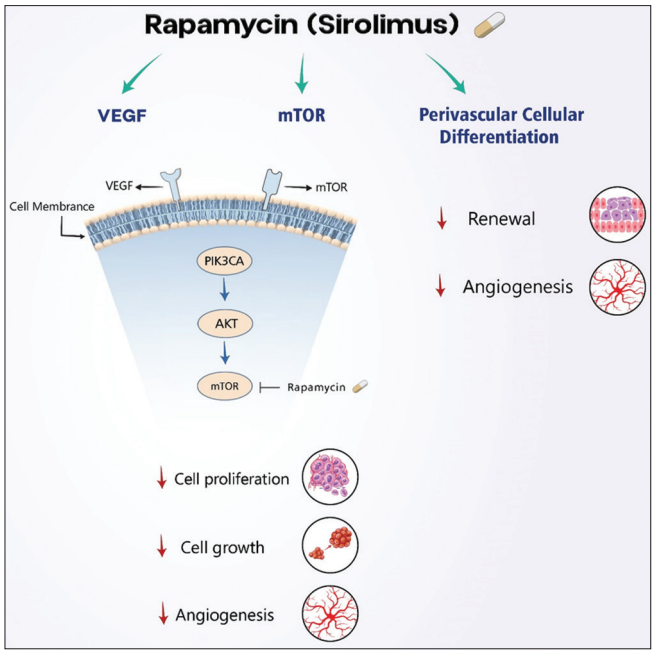


**Figure 2:** Diagram of the potential mechanisms of Rapamycin in the treatment of IH. VEGF: Vascular endothelial growth factor, mTOR: Mammalian target of rapamycin, AKT: Protein kinase B

administration causes the regrowth.[42] Rapamycin may be used as an additive to surgical complement interventional therapy, or as the primary treatment option.[27] Rapamycin therapy was more effective in mucosal areas and lesions near important organs due to a lower likelihood of previous harsh treatment.[28] It is also preferred for treatment resistance to resection, sclerotherapy, propranolol, and steroids by directly suppressing IH stem cells,[14,26,36] whereas it has a lower therapeutic impact on older and more previously treated patients. Another advantage is the milder infection in patients treated by rapamycin according to the Cho *et al*. 2021 study.[28]

Several adverse effects, including mucositis, rash, anorexia, gastrointestinal issues (e.g., diarrhea and nausea), hematologic effects (e.g., thrombocytopenia, leukopenia, and anemia), and metabolic effects (e.g., hyperlipidemia, hyperglycemia, and hypercholesterolemia) have been reported for rapamycin.[43] In the systematic review study, one of the cases developed severe, fatal hypoglycemia after angiography, yet the authors believed it was unlikely that Rapamycin contributed to her demise.[25]

The current systematic review study has some limitations. The number of included studies is limited, and each study reports on a single patient with IH treated with rapamycin, which may reduce the generalizability of the results of the current study. Due to heterogeneity and differences among the reports, conducting a meta-analysis has not been possible, and it seems that studies with a larger number of patients are recommended. The treatment protocols, dosages, and routes of rapamycin administration varied among the included studies. In addition, factors such as genetics, environmental influences, combination therapies, and prior treatments may affect patient outcomes.

## Conclusion

Rapamycin appears to be a safe and effective option for the treatment of IH. Combination therapy, especially in patients resistant to treatment for IH, is a preferred choice for IH treatment and reduces the side effects of propranolol. It is also preferred for the treatment of lesions in the mucosal areas and near important organs.

## Author's Contributions

BAN, EF, FGH, and FA conducted this systematic review. EF formulated the literature search strategy. FGH and EF screened the articles and full texts. EF, FGH, and FA extracted the data and drafted the primary manuscript. BAN produced the initial revision and final drafting. All the authors approved the final version of the manuscript submitted for peer review. EF and BAN have full access to the data and have controlled the decision to publish this work.

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### Conflicts of interest

There are no conflicts of interest.

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43. Napoli KL, Taylor PJ. From beach to bedside: History of the development of sirolimus. Ther Drug Monit 2001;23:559-86.

**Supplementary Table 1: (Search strategy)**

| Search engine | Search strategy | Results |
|---|---|---|
| PubMed | (((((Sirolimus [Title/Abstract]) OR (Everolimus [Title/Abstract])) OR (Rapamune [Title/Abstract])) OR (Macrolids [Title/Abstract])) OR (Rapamycin [Title/Abstract])) AND (((Infant Hemangioma [Title/Abstract]) OR (Hemangioma [Title/Abstract])) | 76 |
| Scopus | ( ( TITLE-ABS-KEY ( sirolimus ) OR TITLE-ABS-KEY ( everolimus ) OR TITLE-ABS-KEY ( rapamune ) OR TITLE-ABS-KEY ( macrolids ) OR TITLE-ABS-KEY ( rapamycin ) ) ) OR TITLE-ABS-KEY ( hemangioma ) OR TITLE-ABS-KEY (infant AND hemangioma) | 428 |
| Web of science | Hemangioma (All Fields) or congenital Skin Neoplasms (All Fields) or Infant Hemangioma (All Fields) AND Rapamune (All Fields) or Rapamycin (All Fields) or Macrolids (All Fields) or Everolimus (All Fields) or Sirolimus (All Fields) | 127 |

**Supplementary Table 2: Quality assessment**

| Articles | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Total score |
|---|---|---|---|---|---|---|---|---|---|
| Oktay, Turkey, 2021 | ! | ! | ✓ | ✓ | ✓ | ✓ | ! | ✓ | 18 |
| Yu Jeong , Korea, 2021 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 24 |
| Fernandez Faith, USA, 2020 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 24 |
| Kelley USA, 2017 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 24 |
| Kaylani England, 2013 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 24 |
| Tole Canada, 2019 | ✗ | ! | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 19 |
| Le Sage Canada, 2019 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 24 |
| Victoria Spain, 2020 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 24 |

JBI critical appraisal tool for case reports. Questions of the checklist are indexed in the table as Q1–Q8, and are written here, Q1) Were patient's demographic characteristics clearly described?, Q2) Was the patient's history clearly described and presented as a timeline?, Q3) Was the current clinical condition of the patient on presentation clearly described?, Q4) Were diagnostic tests or assessment methods and the results clearly described?, Q5) Was the intervention (s) or treatment procedure (s) clearly described?, Q6) Was the post-intervention clinical condition clearly described?, Q7) Were adverse events (harms) or unanticipated events identified and described?, Q8) Does the case report provide takeaway lessons?. Each question is answered in three ways: (Yes= ✓, No= ✗, and Unclear= !