# Burden of Illness in Patients with Facial Angiofibroma Associated with Tuberous Sclerosis Complex: A Systematic Review

HTA64

John D[1], Schachner LA[2], Hebert AA[3], Rai D[1], Majumdar AD[1], **Boggarapu S**[4], Beresford E[4]; [1]*PharmaQuant Insights Pvt. Ltd., Kolkata, India;* [2]*University of Miami Miller School of Medicine, Miami, FL, USA;* [3]*UTHealth McGovern Medical School, Houston, TX, USA;* [4]*Nobelpharma America, LLC, Bethesda, MD, USA*

## BACKGROUND

- Tuberous sclerosis complex (TSC) is a genetic disease caused by mutations in either *TSC1* (hamartin) or *TSC2* (tuberin), genes that regulate cell growth.[1] This rare autosomal dominant disease affects 1 in 5,000 newborns worldwide and 1 in 6,000 newborns in the US.[2,3]
- While TSC presents with multiple manifestations and affects several organs, facial angiofibroma is one of the predominant cutaneous manifestation, affecting 83%-90% of TSC patients.[4]
- Characterizing the burden of illness of a rare condition such as facial angiofibroma associated with TSC is crucial for a better understanding of the disease's overall humanistic and economic burden. Additionally, it aids healthcare providers to make better decisions on clinical management, healthcare policies, and resource allocation.
- Here, we performed a systematic literature review to comprehensively assess the overall epidemiological, humanistic and economic burden of illness of facial angiofibroma associated with TSC.

## METHODS

- The systematic review was conducted per the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA-2020) and the PRISMA-S literature search extension guidelines. PubMed (MEDLINE), Ovid EMBASE, Ovid MEDLINE, Cochrane CENTRAL, EconLit, and Northern Life Sciences Conferences Abstracts, health technology assessment databases, websites, and conferences were searched between March to May 2022. All studies extracted were screened for eligibility by two researchers independently, and any discrepancies were discussed and resolved in consensus with senior team members.
- Studies were included if published in English and if the study population included children (<18 years) or adults (≥18 years) with facial angiofibroma associated with TSC, only when diagnosed by clinicians or any standardized diagnostic tool. Outcomes of interest included epidemiological, humanistic (using health-related quality of life [HRQoL] tools such as generic or disease-specific instruments), and economic (direct medical and non-medical, and indirect costs) measures. Case reports, ecological studies, review articles, letters to the editor, animal studies, or studies based on gene expression were excluded.
- **Table 1** outlines the checklists and guidelines used for data extraction and evaluating the study quality.
- The epidemiological outcome of interest (i.e. proportion of cases of facial angiofibroma associated with TSC) were pooled using a random effects model across populations and diagnostic criteria through the Freeman and Tukey double arcsine transformation to stabilize variance in pooled estimates. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[5] were followed to report the analysis. Forest plots were developed using a random-effects model, and the $I^2$ statistic assessed heterogeneity.
- Funnel plots and Egger's test were used to evaluate publication bias.
- Sensitivity analysis was carried out by excluding one study at a time in the order of publication and sample size, to check for consistency of pooled estimates.

**Table 1. Checklists and guidelines for data extraction and study quality evaluation of various outcomes and study types**

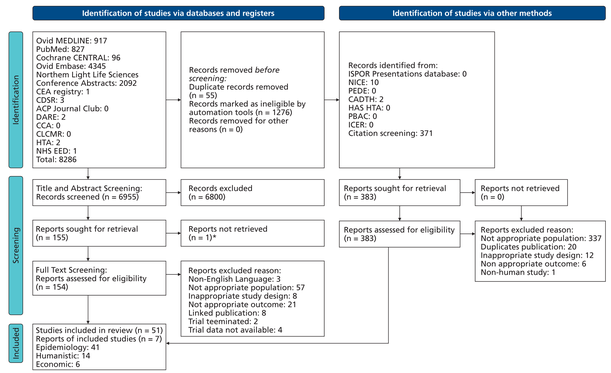
| Outcome/Study type | Guidelines/Checklist Utilized |
|---|---|
| **Data Extraction** | |
| Epidemiological burden | JBI guidelines for incidence/prevalence studies |
| Humanistic burden | Disease-specific patient-reported outcome measures using generic scales, disease-specific scales, direct and indirect valuation methods, preference measures, and qualitative statements |
| Economic burden | CCEMG guidelines and data items included in published studies[6,7] |
| RCT studies | Form based on a publication by Tanvetyanon et al. (2007)[8] |
| Observational studies | Coding form using internal discussions (validated by a few pilot studies) |
| **Study Quality Evaluation** | |
| Observational studies | STROBE checklist |
| Case-series studies | JBI checklist |
| Humanistic studies | Checklist adapted from Huang et al. (2021)[9] for risk of bias |
| RCT studies | Cochrane RoB tool version 2.0 |
| Non-RCT studies | ROBINS-I tool |
| Economic outcomes | CHEC checklist |

*CCEMG, campbell & cochrane economic methods group; CHEC, consensus health economic criteria; JBI, joanna briggs institute; RCT, randomized controlled trial; RoB, risk of bias; ROBINS-I, risk of bias in non-randomized studies of interventions; STROBE, strengthening the reporting of observational studies in epidemiology*

## RESULTS

- Our search identified 8,286 studies, of which 59 related to the epidemiological, humanistic, and economic burden of facial angiofibroma associated with TSC were included. Of the 59 studies, 54 were hospital/clinic-based, while 5 were community/household-based **(Figure 1)**.

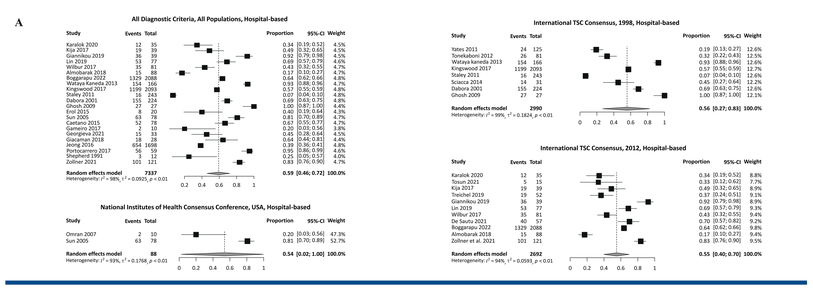
**Figure 1. PRISMA-2020 flowchart**




**1 study not retrieved: conference abstracts unable to retrieve full details for screening.*
*ACP, american college of physicians; CADTH, canadian agency for drugs and technologies in health; CCA, cochrane clinical answers; CDSR, cochrane database of systematic reviews; CEA, cost-effectiveness analysis; CLCMR, cochrane methodology register database guide; DARE, database of abstracts of reviews of effects; HAS, haute autorité de santé; HTA, health technology assessment; ICER, the institute for clinical and economic review; ISPOR, international society for pharmacoeconomics and outcomes research; NHS EED, national health service economic evaluation database; NICE, national institute for health and care excellence; PBAC, pharmacovigilance risk assessment committee; PEDE, pediatric economic database evaluation; PRISMA, preferred reporting items for systematic reviews and meta-analyses*

- Utilizing 10 different criteria for diagnosis of TSC, our review shows 42 studies on epidemiological outcomes on facial angiofibroma associated with TSC. Of these studies, 23 were cohort, 14 cross-sectional, and 5 case series.
- In hospital-based studies, the frequency of patients having facial angiofibroma associated with TSC was between 7%-95% **(Figure 2A)**, while in community-based studies, the frequency was 4%-86% **(Figure 2B)**. The pooled proportion across all diagnostic criteria was 59% (46%-72% confidence interval [CI]) and 50% (19%-81% CI) in hospital- and community-based studies, respectively **(Figure 2)**.
- Significant heterogeneity was observed in the pooled estimates across all diagnostic criteria for both hospital-based ($p < 0.01$; $I^2 = 98\%$; $\tau^2 = 0.0925$) and community-based ($p < 0.01$; $I^2 = 97\%$; $\tau^2 = 0.1225$) studies **(Figure 2)**.

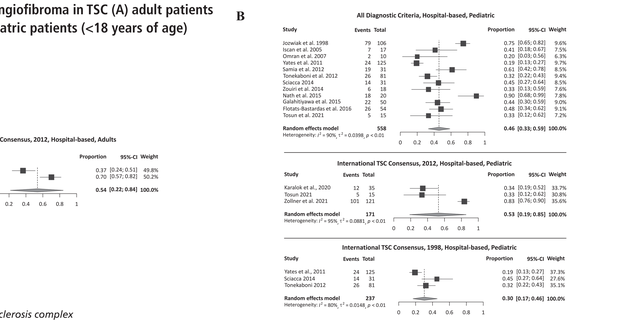
**Figure 2. Frequency of facial angiofibroma in TSC patients across (A) hospital-based studies, and (B) community-based studies**




*CI, confidence interval; TSC, tuberous sclerosis complex*

- In hospital-based studies, the proportion of patients with facial angiofibroma associated with TSC was between 37%-70% across adults **(Figure 3A)** and 19%-90% across children **(Figure 3B)**.

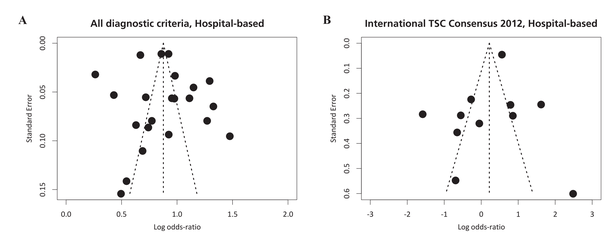
**Figure 3. Proportion of facial angiofibroma in TSC (A) adult patients (≥18 years of age) and (B) pediatric patients (<18 years of age) across hospital-based studies**




*CI, confidence interval; TSC, tuberous sclerosis complex*

- The funnel plots of hospital-based studies **(Figure 4)** were symmetrical, indicating no publication bias. This information complemented the results from Egger's test (insignificant at a significance level of 5%).

**Figure 4. Funnel plot of hospital-based studies across (A) all diagnostic criteria and (B) using International TSC Consensus 2012 criteria**




*TSC, tuberous sclerosis complex*

- In the sensitivity analysis, the estimated pooled proportions were consistent using leave-one-out in the order of publication and sample size for diagnostic criteria of TSC by the International TSC Consensus (1998).[10]
- Mortality burden was reported in 7 epidemiological studies.[11-17] However, mortality data were unrelated to facial angiofibroma but related to the underlying causes due to TSC.
- Fourteen studies[18-31] (2 cohort, 2 cross-sectional, 4 randomized controlled trials [RCTs], 1 non-RCT, and 5 case-series), all hospital-based, reported the humanistic burden of patients with facial angiofibroma related to TSC, of which 8 reported no association with a significant humanistic burden. However, since the humanistic burden was assessed using different HRQoL tools across literature, the assessment of burden in this patient population appears complex for comparison.
- Six studies[19,22,32-35] reported the economic outcomes of facial angiofibroma associated with TSC (2 cohort, 1 cross-sectional, 2 case series, and 1 case report), of which 5 presented direct costs related to sirolimus 0.1%. The annual cost of treatment with sirolimus 0.1% ranged between $2,458.58 and $13,112 (adjusted to the value of the US dollar for the year 2021).
- The quality of cohort studies ranged from low to high, while most cross-sectional studies were of low/moderate quality, and only one case-series was of low quality.

## CONCLUSIONS

- This is the first systematic review to comprehensively estimate the epidemiological, humanistic, and economic burden of illness in patients with facial angiofibroma associated with TSC.
- Our review identified critical evidence gaps in the published literature assessing the burden of illness of facial angiofibroma associated with TSC. There is a need for comprehensive real-world evidence strategy to understand the actual disease burden associated with the condition.

**ACKNOWLEDGEMENTS & DISCLOSURES:** Nobelpharma America, LLC, USA, funded this work. The study sponsor was involved in several aspects of the research, including study design, the interpretation of the data, and the production of the poster. The study was conducted by PharmaQuant Insights Pvt. Ltd., India. The authors thank SciVoc Consulting Inc., Toronto, Canada, for providing editing support for the poster.

**REFERENCES: 1.** Orlova KA, et al. Ann N Y Acad Sci 2010;1184:87-105. **2.** Zöllner JP, et al. Orphanet J Rare Dis 2020 5;15(1):141. **3.** TSC Alliance. About TSC. https://www.tscalliance.org/about-tsc/what-is-tsc/. **4.** Portocarrero LKL, et al. An Bras Dermatol 2018;93(3):323-331. **5.** Brooke BS, et al. JAMA Surg 2021;156(8):787-788. **6.** The Campbell and Cochrane Economics Methods Group (CCEMG). CCEMG-EPPI-Centre Cost Converter. https://eppi.ioe.ac.uk/costconversion/default.aspx. **7.** Aluko P, et al. Chapter 20: Economic evidence. 2021. In: Higgins JPT, et al. Cochrane Handbook for Systematic Reviews of Interventions. Wiley Blackwell; 2019. 507-522 **8.** Tanvetyanon T, et al. J Thorac Oncol 2007;2:1091-97. **9.** Huang J, et al. Arch Dermatol Res 2021;314(5):445-62. **10.** Roach ES, et al., J Child Neurol 1998 13(12):624-8. **11.** Ahlsen ICG, et al. Arch Neurol 1994;51:76-81. **12.** Charles WV, et al. Arch Neurol 1991;48:400-1. **13.** Galahitiyawa J, et al. Sri Lanka J Child Health 2015;44(2):97-102. **14.** Kija E, et al. S Afr Med J 2017;107(6):295-8. **15.** Ohno K, et al. Brain Dev 1981;3(1):57-64. **16.** Wiederholt WC, et al. Neurology 1985;35(4):600-603. **17.** Zouiri G, et al. J Pediatr Neonatal Care 2014;1(5). **18.** Ali FR, et al. J Cosmet Laser Ther 2016;18(7):372-375. **19.** Amin S, et al. Int Sch Res Notices 2017;2017:8404378. **20.** Boixeda P, et al. J Pediatr Dermatol 2016;33(5):518-25. **21.** Chen PL, et al. Br J Dermatol 2020;183(4):655-63. **22.** Crall C, et al. Pediatr Dermatol 2016;33(5):518-25. **23.** De Sautu De Borbon EC, et al. Orphanet J Rare Dis 2021;16(1):243. **24.** Hatano T, et al. Orphanet J Rare Dis 2020;15(1):133. **25.** Koenig M, et al. JAMA Dermatology 2018;154(7):773-80. **26.** Ott J, et al. Int J Clin Pharm 2013;35(6):1331. **27.** Papadavid E, et al. Br J Dermatol 2002;147:337-42. **28.** Viswanath V, et al. Indian J Dermatol 2016;61(1):119. **29.** Wataya-Kaneda M, et al. JAMA Dermatol 2017;153(1):39-8. **30.** Wataya-Kaneda M, JAMA Dermatology 2018;154(7):781-8. **31.** Wataya-Kaneda M, et al. Dermatol Ther (Heidelb) 2020;10(4):635-50. **32.** Foster RS, et al. Aust J Dermatol 2012;53:52-6. **33.** Norrenberg S, et al. Br J Dermatol 2018;179(1):208-9. **34.** Pynn EV, et al. Pediatr Dermatol 2015;32(3):e120-23. **35.** Smith EV, et al. Br J Dermatol 2012;167(Suppl. 1):129.