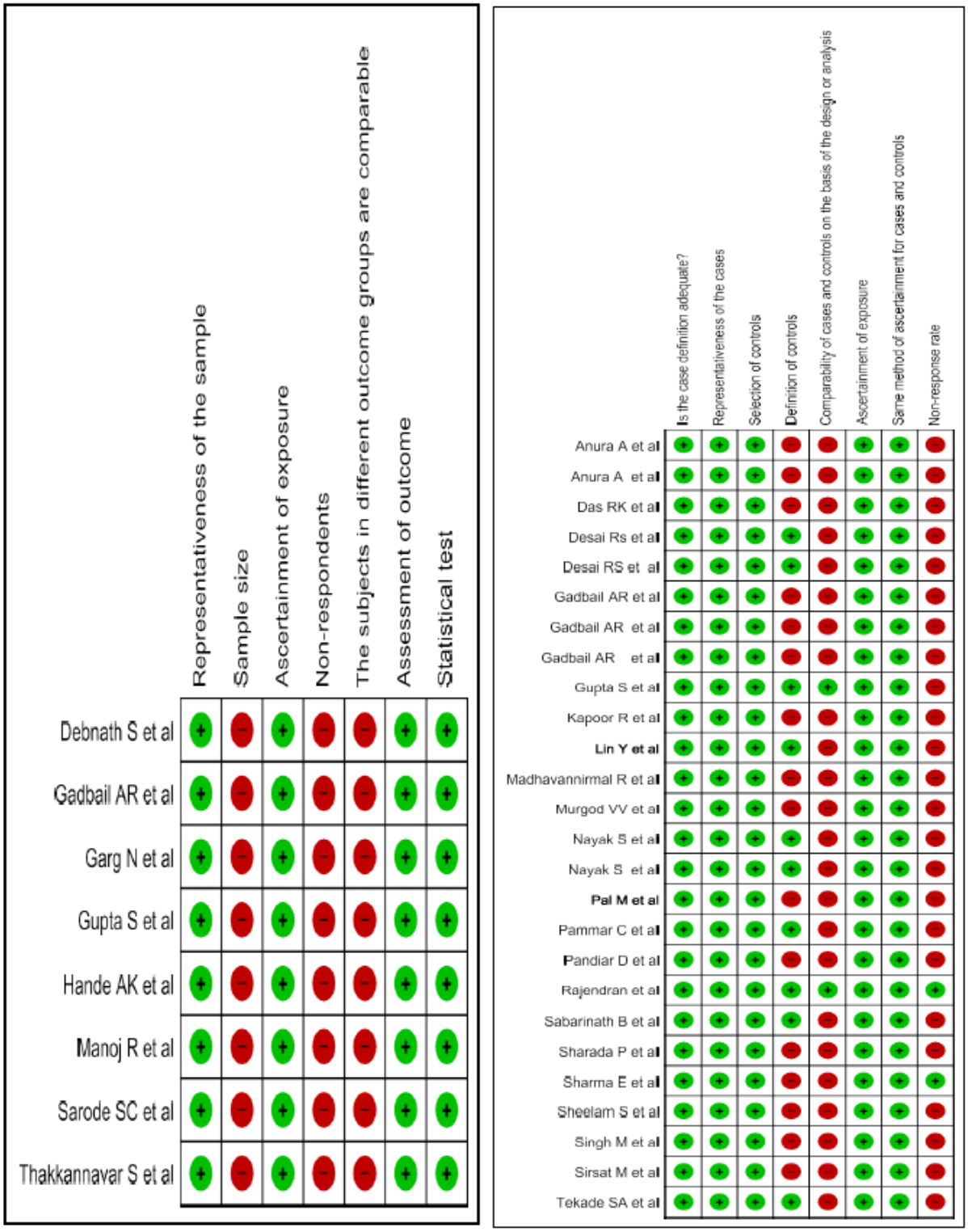
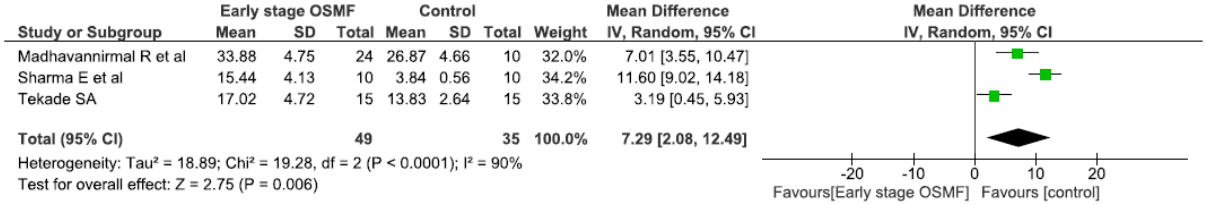
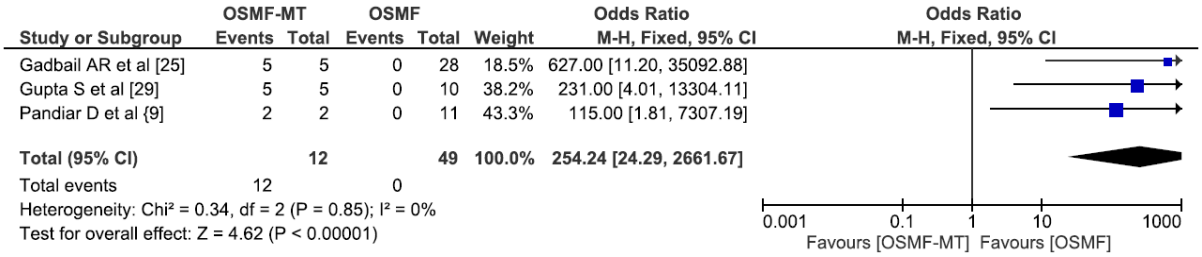


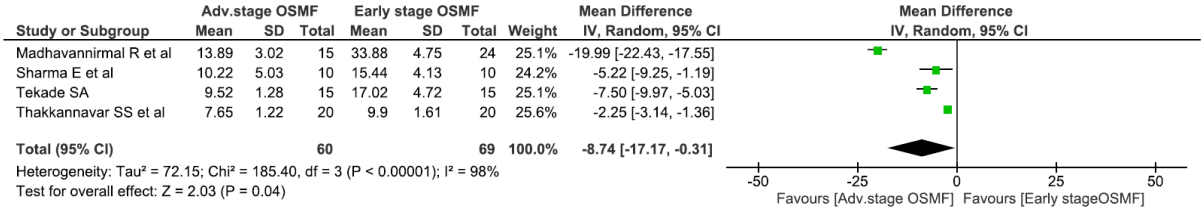
Supplementary Fig. 1. Summary of the risk of bias of the included case-control and cross-sectional studies, based on the modified Newcastle–Ottawa scale approach.



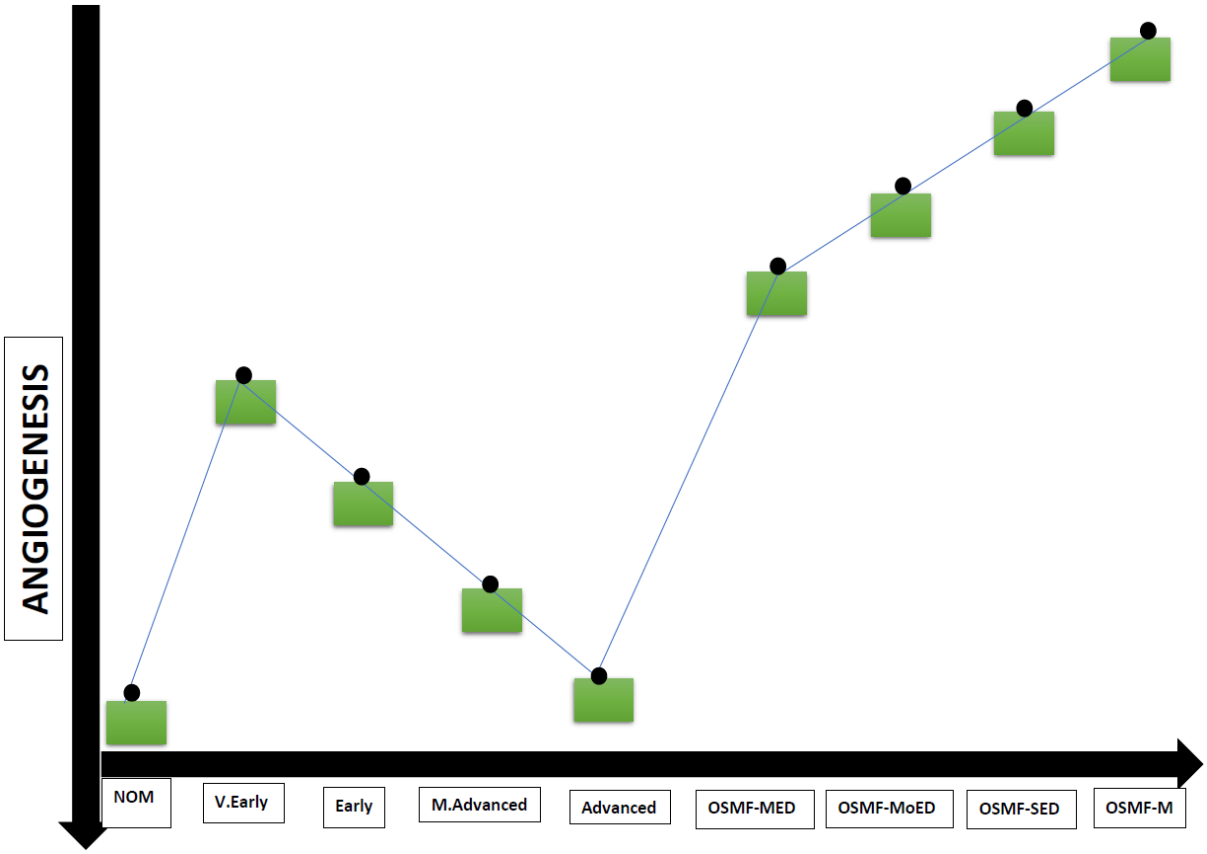
Supplementary Fig. 2. Forest plot of absolute early-stage fibrosis risk of OSMF cases associated with significant angiogenesis expression (random-effects model: combined mean difference, 7.29; 95% CI, 2.08-12.49; *P*=0.006 with substantial heterogeneity). (OSMF: oral submucous fibrosis, SD: standard deviation, CI: confidence interval)



Supplementary Fig. 3. Forest plot of absolute malignant transformation risk of OSMF cases associated with significant angiogenesis expression (fixed-effects model: combined mean difference, 523.83; 95% CI, 125.74-2182.28; *P*<0.00001 with null heterogeneity). (OSMF: oral submucous fibrosis, CI: confidence interval, MT: malignant transformation)



Supplementary Fig. 4. Forest plot of absolute advanced-stage fibrosis risk of OSMF cases associated with significant angiogenesis expression (random-effects model: combined mean difference, −8.74; 95% CI = −17.17 to −0.31; *P*=0.04 with substantial heterogeneity). (OSMF: oral submucous fibrosis, SD: standard deviation, CI: confidence interval)



Supplementary Fig. 5. Graphical interpretation of angiogenesis in the progression of fibrosis of OSMF and its malignant transformation. (NOM: normal oral mucosa, V: very, M: moderately advanced, OSMF-MoED: oral submucous fibrosis-moderate epithelial dysplasia, SED: severe epithelial dysplasia)

Supplementary Table 1. Search strategies for various databases

Database	Syntax
PubMed	(“microvascular density”[MeSH Terms] OR “microvascular density”[tiab] OR angiogenesis[tiab] OR “microvessel density”[MeSH Terms] OR “microvessel density[tiab] OR mean vascular density[tiab] OR(“neovascularization”[MeSH Terms] OR “neovascularization”[tiab] OR vascular endothelial growth factors”[MeSH Terms] OR “vascular endothelial growth factors”[tiab] OR “platelet endothelial cell adhesion molecule-1”[MeSH Terms] OR “platelet endothelial cell adhesion molecule-1”[tiab] OR PECAM-1[tiab] OR CD31[tiab] OR CD34[tiab] OR “vascular cell adhesion molecule-1”[MeSH Terms] OR “vascular cell adhesion molecule-1”[tiab] OR VCAM-1[tiab] OR “CD106”[tiab] OR adhesion molecules[tiab] OR vascular adhesion molecules[tiab] OR “intercellular adhesion molecule-1”[tiab] OR “intercellular adhesion molecule-1”[MeSH Terms] OR ICAM-1[tiab] OR “endoglin”[MeSH Terms] OR endoglin[tiab] OR CD105[tiab] OR “factor VIII related antigen”[MeSH Terms] OR “factor VIII related antigen”[tiab])AND (“oral submucous fibrosis”[MeSH Terms] OR “oral submucous fibrosis”[tiab] OR “oral oral submucous fibrosis with dysplasia”[tiab] OR “oral oral submucous fibrosis with malignant transformation”[tiab]) AND (“immunohistochemistry”[MeSH Terms] OR “immunohistochemistry”[tiab] OR “blotting, western”[MeSH Terms] OR “blotting, western”[tiab] OR western blot[Text Word] OR “polymerase chain reaction”[MeSH Terms] OR polymerase chain reaction[tiab] OR “trichrome stain”[All Fields] OR trichrome stain[Text Word])
Cochrane Library	ID Search hits #1 MeSH descriptor: [oral submucous fibrosis] explode all trees 57 #2 MeSH descriptor: [angiogenic markers] in all MeSH products 73 #3 (IHC/blotting western/RT-PCR):ti,ab,kw AND (oral submucous fibrosis):ti,ab,kw 8 #4 (angiogenesis):ti,ab,kw AND (oral submucous fibrosis):ti,ab,kw 2 #5 #2 or #4 40 #6 #1 or #3 or #5 180
Google Scholar	ALL (“microvascular density” OR “angiogenesis” OR “microvessel density” OR “Mean vascular density” OR “morphometry” OR “vascular endothelial growth factors” OR “platelet endothelial cell adhesion molecule-1” OR “PECAM 1” OR “CD31” OR “CD34” OR “vascular cell adhesion molecule-1” OR VCAM-1” OR “CD106” OR “adhesion molecules” OR “vascular adhesion molecules” OR “intercellular adhesion molecule-1” OR “ICAM-1” OR “endoglin” OR “CD105” OR “Factor VIII related antigen” OR “Vascularity” OR “neoangiogenesis” OR “VEGF” OR “VEGFRII”) AND ALL (“oral submucous fibrosis” OR “Precancer” OR “Potentially malignant disorders” OR “OSMF with dysplasia” OR “OSMF with malignant transformation”) AND ALL (“immunohistochemistry” OR “polymerase chain reaction” OR “Masson’s trichrome stain” OR “special stain” OR “western blot” OR “IHC” OR “RT-PCR”)

Supplementary Table 2. Studies included for haematoxylin and eosin assessment of angiogenesis in oral submucous fibrosis

S. No	Authors, year/ Country	Study Type	Sample size			Staining used/ method and Tissue section employed	Parameter used/ Magnification & Field	Outcome	p value	Study Inferences
			Total	OSMF	Control					
1.	Rajendran R et al[13], 2005/India	Case-control	30	20 OSMF	10 NOM	H&E/FFPETS/Quan/ Digital analysis	1.Mean vascular density (MVD) 2.Mean vascular area percentage (MVAP) 3. Mean vascular luminal diameter (MVLD)	The MVD is found to be more or less same in the OSMF and control samples.[a] The MVPA shows an increasing trend as the disease progresses.[b] The MVLD also shows an increasing trend as the disease progresses. [c]	a>0.05 b<0.01 c<0.01	This study demonstrates that mean vascular dilatation noted is assumed to be an adaptive response to compensate tissue ischaemia/hypoxia. The usual tissue reaction resultant to ischemia/ hypoxia does not seem to operate in this disease, which is preconditioned by significant stromal changes as part of the disease process.
2.	Garg N et al[14], 2014/ India	Case-control	45	35 OSMF 7 Vey early 14 Early 9 Moderately 5 Advanced (Pindborg and Sirsat 1966 OSMF grading criteria)	10 NOM	H&E/FFPETS/Quan/ Digital analysis	1.Mean blood vessel area (MBVA) 2.Mean blood vessel diameter (MBVD) 3.Mean blood vessel perimeter (MBVP)	MBVA[a] Control 3280.50±550.87 Grade I 3257.23±1496.37 Grade II 3860.25±872.40 Grade III 3153.06±552.32 Grade IV 2807.48±511.51 MBVD[b] Control. 61.18±10.04 Grade I. 58.87±5.57 Grade II 61.57±16.87 Grade III 56.94±9.34 Grade IV 56.29±4.16 MBVP[c] Control 251.33±88.68 Grade I 241.33±334.33 Grade II 260.80±82.38 Grade III 254.45±59.90 Grade IV 226.74±28.82	a-0.55 b-0.83 c-0.90	These findings question the role of ischemia in the aetiopathogenesis of OSMF.
3.	Singh M et al[16], 2010/ India	Cross-sec	83	83 OSMF Grade I 9 Grade II 32	NA	H&E/FFPETS/Quan/ Digital analysis	1.Number of endothelial cells (EC) per low power field (10X) (directly proportional to the number of blood	OSMF I II III IV EC 409.2 252.6 208.7 85.7 BVA 33.6 575.2 161.0 7.8		This study concluded that mean blood vessel area and the mean vessel

				Grade III 39 Grade IV 3 (Pindborg and Sirsat 1966 OSMF grading criteria)			vessels) 2.Mean blood vessel area (BVA) (10X) 3.Average mean diameter (AMD) of the blood vessels (40X)	AMD 5.6 13.0 8.5 1.0		diameter showed a marked increase in grade II and a marker decrease in grade IV and the grade III and number of endothelial cells per low power field consistently decreased with the increasing grades of OSMF. The luminal diameter in grade IV showed near obliteration of the lumen.
4.	Sarode SC et al[17], 2021/ India	Cross-sec	38	38 OSCC with OSMF	NA	H&E/Analysed mucosal surgical margins of 38 OSCC with OSMF	22 (57.89%) showed conspicuous large dilated vascular spaces lined by endothelial cells. In all the cases, these large dilated spaces were engorged with red blood cells and were located at the juxta-epithelial and submucosal regions.	Vascular spaces/HPF 7.31±4.88	NA	This study emphasizes that conspicuous and frank dilated vascular spaces as a marker of malignant transformation in OSMF.
5.	Pal M et al[18],2020/ India	Case-control	46	36 OSMF 10 OSMFW-ED 26 OSMFWT-ED	10 NOM	H&E/FFPETS/Quan/ Digital analysis	Ratio of vasculature in juxta-epithelial connective tissue [i.e., area covered by blood vessels/total area] (20X)	Ratio of vasculature NOM 0.13±0.02[a] OSMFW-ED 0.09±0.02[b] OSMFWT-ED 0.16±0.02[c]	a-b-c <0.001	This result demonstrates that ratio of vasculature in juxta-epithelial connective tissue might reflect the change in the oral mucosa which is conducive for the transformation of precancer into malignancy.
6.	Debnath S et al[19], 2013/ India	Case-control	100	OSMF 100 36 Vey early 29 Early 28 Moderately 7 Advanced (Pindborg and Sirsat 1966 OSMF grading criteria)	NA	H&E/FFPETS/Quan/ Digital analysis	1. Blood vessel density (10X) (number of endothelial cells per square micron of the subepithelial zone) 2. Mean blood vessel area (10X) 3. Average mean luminal diameter of the blood vessels (40X) (MVLD)	No. of endothelial cells[a] Grade I 410.0667[a1] Grade II 251.6566[a2] Grade III 211.5667[a3] Grade IV 85.6666[a4] Mean Blood vessel area[b] Grade I 31.5038 Grade II 585.1401 Grade III 164.2813 Grade IV 7.7992 Blood vessel mean luminal Diameter[c] Grade I 5.8996	a< 0.001 a1-a2 >0.05 a3-a4 0.001 b< 0.001 c< 0.001	This study concludes that it might be in the initial stages there is an increase in the number of blood vessels along with dilatation and congestion – early stage showing highest dilatation. At the later advanced stages probably, these mechanisms become decompensated due to persistent insults resulting

								Grade II 11.8592 Grade III 8.0659 Grade IV 0.9818		in constriction or near obliteration of the blood vessels along with a decrease in their number.
7.	Kapoor R et al[20], 2022/ India	Case-control	60	OSMF 30 Mild ED 11 Mod ED 13 Sevr ED 6	30 NOM	H&E/FFPETS/Quan/ Digital analysis	Mean Vascular density (MVD)- 3 fields (40X)	MVD[a] OSMF 3.89±2.24 Controls 3.76±2.88 Epithelial dysplasia and vascularity[b] Mild 11 3.42±2.89 Mod 13 4.51±1.93 Severe 6 3.39±1.26 There was a slight and positive correlation between vascularity and fibrosis and vascularity and epithelium thickness.[c]	a-0.84 b-0.42 c>0.05	This result concludes that epithelial thickness, fibrosis, and vascularity did not have a significant relationship with epithelial dysplasia.
8.	Murgod VV et al[21],2014/ India	Case-control	100	OSMF 60 Early 30 Advanced 30 WDSCC 30 (Pindborg and Sirsat 1966 OSMF grading criteria)	NOM 10	H&E/FFPETS/Quan/5 fields;40X/Digital analysis	1. Mean vascular density (MVD) 2. Mean vascular luminal diameter (MVLD) 3. Mean vascular area (MVA) 4. Mean vascular percentage area (MVPA)	MVD[A] Control 8 ± 2.26[a] OSMF 11.35 ±4.34[b] WDSCC 18.99 ± 6.04[c] EOSMF[b1] AOSMF[b2] MVLD[B] Control 99.7-153.1µm (mean 120.46µm)[a] OSMF 84.31-189.49µm (mean 124.94 µm)[b] WDSCC 88.12-205.76µm (mean 137.90 µm)[c] EOSMF[b1] AOSMF[b2] MVA[C] Control 14,718±5728.8µm^{2a} OSMF 16297 ± 6955.1µm^{2b} WDSCC 20537 ± 9251.7µm^{2c} EOSMF[b1] AOSMF[b2] MVPA[D] Control[a] OSMF[b] WDSCC[c] EOSMF[b1] AOSMF[b2]	b>a=<0.05 b-c=0.000 b>a=<0.05 b-c=0.05 b>a=<0.05 b-c=0.044 b>a=<0.05 b-c=0.00	This result shows that vascularity was increased in early OSMF and reduced in advanced OSMF, suggesting that inflammation may play a role in the early stages while progressive fibrosis may predispose to atrophy of the epithelium and subsequent malignant changes.

								MVD, MVLD, MVA and MVAP increased from control to EOSMF, decreased in AOSMF, and increased again in WDSCC.[E] Normal mucosa and AOSMF showed no significant differences in any of the parameters. Significant differences in MVD and MVAP were evident between control and EOSMF, control and WDSCC, EOSMF and AOSMF, and EOSMF and WDSCC; the AOSMF and WDSCC groups demonstrated significant differences in all of the parameters.	E<0.001	
9.	Sirsat SM et al[22],1967/ India	Case-control	137	124 OSMF 4 very early stage 61 early stage 50 moderately advanced 9 advanced stage (Pindborg and Sirsat 1966 OSMF grading criteria)	13 NOM	H&E/FFPETS/Qual	1.Normal (N) 2.Normal/dilated (N/D) 3.Dilated (D) 4.Dilated/constricted (D/C) 5.Normal/constricted (N/C) 6.Constricted (C)	State of blood vessels N N/D D D/C N/C C VES 0 0 4 0 0 0 ES 9 1 54 10 0 0 MD 0 6 13 22 6 6 ADV 0 0 1 6 1 1 Ctrl 10 0 2 1 1 1		This study observed extreme dilatation in the early stages and narrowing in the more advanced stages. The persistent dilatation seen in many moderately advanced and advanced biopsies also merits some comment. The constriction of the mucosal blood vessels is therefore an obvious result of the increasing pressure exerted by the densely fibrous or frankly hyaline environment.

(OSMF: oral submucous fibrosis, OSCC: oral squamous cell carcinoma, WDSCC: well differentiated squamous cell carcinoma, NOM: normal oral mucosa, H&E: hematoxylin and eosin, Quan: quantitative, Qual: qualitative, FFPETS: formalin fixed paraffin embedded tissue section, NA: not available, OSMFW-ED: oral submucous fibrosis with epithelial dysplasia, OSMFWT-ED: oral submucous fibrosis without epithelial dysplasia, Mild ED: mild epithelial dysplasia, Mod ED: moderate epithelial dysplasia, Sevr ED: severe epithelial dysplasia, MVD: mean vascular density, MBVA: mean blood vessel area, MBVD: mean blood vessel diameter, MBVP: mean blood vessel perimeter, MVLD: mean vascular luminal diameter)

Supplementary Table 3. Studies included for immunohistochemical assessment of angiogenesis in Oral Submucous Fibrosis

S. No	Authors, year/ Country	Study Type	Sample size			IHC markers used/ method and Tissue section employed	Magnification & Field	Outcome	p value	Study Inferences
			Total	OSMF	Control					
1.	Pandiar D et al[9], 2014/India	Case-control	47	OSMF 30 11 Early 17Moderately advanced 2 Advanced 5OSMF with dysplasia 2 OSMF with OSCC (Pindborg and Sirsat 1966 grading criteria)	10 NOM	CD34-monoclonal/FFPETS /Quan-MVD	3 hotspots, 40X	MVD[A] Early 20.48 Moderately advanced 17.40 Advanced 14.85 OSMF with dysplasia 22.04 OSMF with OSCC 42.30 Control 42.08	A-0.000	This study shows observation of decreased vascularity in different stages of OSMF and the significant relationship of epithelial thickness with the stages of OSMF reiterates the prevailing concept that lack of perfusion leads to epithelial atrophy, which may later undergo dysplastic changes and turn malignant as evidenced by increased vascularity in OSMF with dysplasia and OSCC.
2.	Thakkannavar SS et al[10], 2019/India	Cross-sectional	40	OSMF 40 Early 20 Advanced 20 (Pindborg and Sirsat 1966 grading criteria)	NA	Factor-VIII/monoclonal/ FFPETS/quan-MVD	5 fields/ 40X	MVD EOSMF 9.9± 1.61[a] AOSMF 7.65± 1.22[b]	a-b0.00	This result shows that in advanced cases of OSMF the vascularity is reduced which may predispose to epithelial atrophy and subsequent malignant changes.
3.	Tekade SA et al[11], 2017/India	Case-control	55	OSMF 45 stage 1 >30mm stage 2 30-21mm stage 3 <20mm (Lai DR et al 1995 grading criteria)	15 NOM	CD34 monoclonal-MVD, TVA and MVA/FFPETS	3 hotspot fields, 40X	MVD[A] stage 1 17.02±4.72 stage 2 12.80±2.61 stage 3 9.52±1.28 NOM 13.83±2.64 TVA[B] stage 1 2876.73±1381.36 stage 2 1996.57±886.37 stage 3 608.56±160.34 NOM 3579.13±1608.28 MVA[C] stage 1 187.25±119.11 stage 2 160.00±75.76 stage 3 65.41±21.40 NOM 251.82±98.94	A<0.001 B<0.001 C<0.001	This result shows that angiogenesis is seen in early stages of OSMF with decreasing trend in advanced stages. Decreased vascular areas seen in advanced stages could be attributed to the increasing fibrosis surrounding the blood vessels.
4.	Madhavan Nirmal R et al[12], 2016/India	Case-control	75	65 OSMF EARLY 24 Early-WD 13 Early-D 8 Early-M 3 INTERMEDIATE	10 NOM	CD34- MVD,VEGF1-semiQuan/FFPETS	MVD-3hotspots,20X VEGF (Epi/Inf/Endothe)	MVD Control 26.87±4.66[b] OSMF 24.73±9.53[a] Grade 1 33.88±4.75[a1] Grade 2 22.54±7.12[a2] Grade 3 13.89±3.02[a3]	a-b>0.05 a1-a2-a3<0.05	This result demonstrates that epithelial secreted VEGF could possibly play a pivotal role in either sustaining or stimulating angiogenesis that support tumour growth and invasion in OSMF

				26 Interm-WD 14 Interm-D 10 Interm-M 2 ADVANCED 15 Advanced-WD 8 Advanced-D 7 Advanced-M 0 (Utsunomiya et al 2005 grading criteria)				OSMFWT-ED 23.19±9.35[a4] OSMFW-ED 24.04±8.25[a5] OSMF-MI 38.93±5.14[a6] VEGF Pos% Neg % Control 3(30.0) 7(70.0)[b] OSMF 34(52.3 31(47.7)[a] Grade 1 13(54.2) 11(45.8)[a1] Grade 2 13(50.0) 13(50.0)[a2] Grade 3 5(33.3) 10(66.7)[a3] OSMFWT-ED 23(65.7) 12(34.3)[a4] OSMFW-ED 8(32.0) 17(68.0)[a5] OSMF-MI 0(0) 5(100)[a6] VEGF. Staining intensity Control 0.3±0.5[b] OSMF. 0.9±1[a] Grade 1 0.8±1[a1] Grade 2 0.8±0.9[a2] Grade 3 1.3—1.1[a3] OSMFWT-ED 0.5±0.7[a4] OSMFW-ED 1.1±1[a5] OSMF-MI 2.6±0.6[a6]	a4-a5-a6<0.05 a-b>0.05 a1-a2-a3>0.05 a4-a5-a6=0.003 a-b>0.05 a1-a2-a3>0.05 a4-a5-a6=0.00	patients.
5.	Hande AH et al[24], 2022/India	Cross-sectional	203	OSCC with OSMF (Group I) 102 OSCC (Group II) 101	NA	CD105-monoclonal/ Quan-MVD/ FFPETS	3 hotspots, 10X	CD105[A] Group I-8.88 ± 3.41[a1] Group II-16.13 ± 5.86[a2] CD105 & grades of OSCC[B] WDSCC[b1] Group I 8.30±3.01 Group II 14.65±5.40 MDSCC[b2] Group I 31-9.81±4.24 Group II 58-16.58±5.93 PDSCC[b3] Group I 7- 10.09±1.13 Group II 10- 18.39±6.27 CD105 & Clinical "TNM Staging[C] Early stage[c1] Group I 49- 8.18±3.32 Group II 18- 15.05±6.50 Advanced stage[c2] Group I 53- 9.53±3.40 Group II 83- 16.36±5.72 CD105 & lymph node metastasis[D] Positive 48[d1] Group I - 9.11±2.77 Group II- 17.89±5.73 Negative 53[d2] Group I 7- 8.78±3.68	a1-a2<0.0001 b1<0.0001 b2<0.0001 b3-0.004 c1<0.0001 c2<0.0001 d1<0.0001 d2<0.0001	This result demonstrates the assessment of neoangiogenesis using CD105 can be an important prognostic marker which may help in distinguishing between OSCC with (Group I) and without OSMF cases (Group II).

								Group II 10- 14.53±5.55		
6.	Gadbail AR et al[25],2019/India	Case-control	185	OSMF 50 OSCC with OSMF 105	30 NOM	CD105/quan-MVD/FFPETS	3 hot spot fields, 10X	CD105 MVD NOM 30 3.53±5.17[a] LRED 28 27.78±11.80[b] HRED 22 46.18 ±12.55[c] WDSCC 63 65.63±8.20[d] MDSCC 37 85.78±11.47[e] PDSCC 5 99.00±13.07[f]	a < b =<0.001 b< c = <0.001 c < d = <0.001 d < e = <0.001 e< f = 0.018	This result shows that CD105 expression alone or together correspond with the disease progression model of OSMF. Hence, expression of these markers can be used as a predictive marker of clinical outcome of OSCC-OSMF.
7.	Gadbail AR et al[26],2017/India	Case-control	79	49 OSMF LRED 27 HRED 22	30 NOM	CD105/MVD/ FFPETS	2 hotspots, 10X	CD105 LRED 22.08±12.27[a1] HRED 47.28±13.39[a2] Control 3.53±5.17[b]	a1-a2-b=0.000	This result demonstrates that expressions of ki67, CD105 and α-SMA markers compliment binary grading system of OED in OPMDS, thus justifying its use in clinical practice.
8.	Gadbail AR et al[27],2018/India	Case-control	80	50 OSMF	30 NOM	CD105/quan-MVD/FFPETS	2 hot spot fields, 10X	MVD LRED 27.57±12.25[a1] HRED 46.18±12.55[a2] Control 3.53±5.17[b]	a1-a2-b<0.0001 a2>b a3>b	This result shows that CD105 expression showed significant differences between normal, LRED and HRED. These findings further support that features such as increased basal cell layer hyperplasia, abnormal superficial mitosis, increased nuclear-cytoplasmic ratio, and hyperchromasia could be transformation-relevant dysplastic features.
9.	Gadbail AR et al[28],2020/India	Cross-sectional	217	OSCC with OSMF 105 OSCC 112	NA	CD105/quan-MVD/FFPETS	2 hot spot fields, 10X/Invasive front area	MVD[A] OSCC with OSMF 74.32±14.62[a] OSCC 82.44±14.34[b] WDSCC[B] OSCC with OSMF 65.63±8.20[a] OSCC 73.94±10.90[b] MDSCC[C] OSCC with OSMF 85.78±11.47[a] OSCC 85.36±13.51[b] PDSCC[D] OSCC with OSMF 99.00±13.07[a] OSCC 101.33±12.24[b] Early clinical TNM stage[E] OSCC with OSMF 67.62±12.01[a] OSCC 74.85±14.33[b] Advanced clinical TNM stage[F] OSCC with OSMF 79.96±14.33[a] OSCC 84.09±13.88[b] Non-metastatic[G]	A<0.001 B<0.001 C=0.905 D=0.714 E=0.059 F=0.05 G<0.001	This study is the first of its kind to attempt to investigate the biological distinctness of OSCC-OSF. This unique malignancy showed significantly less expression of *CD105* compared to conventional OSCC.

								OSCC with OSMF 69.52±11.38[a] OSCC 77.40±13.28[b] Metastatic[H] OSCC with OSMF 86.89±14.87[a] OSCC 89.42±12.86[b] Survived>3yrs[I] OSCC with OSMF 70.10±11.75[a] OSCC 77.69±13.94[b] Survived<3yrs[J] OSCC with OSMF 89.34±14.17[a] OSCC 89.26±12.09[b]	H=0.335 I=0.001 J=0.794	
10.	Gupta S et al[29],2022/India	Case-control	15	10 OSMF 5 OSMF with OSCC (Khanna JN and Andrade NN 1995 grading system)	NA	Factor VIII-monoclonal/ FFPETS/Quan-MVD	3 hotspots; 10X	MVD OSMF 13.74±3.26[a] Mod Adv 13.20±3.20[a1] Adv 14.29±3.61[a2] OSMF-M 17.03±2.03[b]	a-b=0.318 a1-a2-b<0.05	This result shows that molecular mechanisms responsible for the development of OSCC in patients with OSMF require unification of multiple progressive pathogenetic mechanisms (angiogenetic response) involved in the progression of the disease.
11.	Sheelam S et al[30],2018/India	Case-control	20	10OSMF	10 NOM	VEGF (Connective tissue)-semiQuan;CD34-MVD/ FFPETS	10X; 3 hotspot,40X	VEGF[A] OSMF 2.4000±0.51640[a] Control 1.0000±0.00[b] CD34[B] OSMF 32.8000±3.65[a] Control 7.40000±1.17[b]	A-0.000 B-0.000	This result demonstrates that upregulation of cell proliferation and vascularity indicates their possible role in malignant transformation of potentially malignant disorders.
12.	Anura et al[31], 2014/India	Case-control	68	58 OSMF 18 OSMFWT-ED 40 OSMFW-ED OSMFMLD OSMFMOD OSMFSEVD	10 NOM	VEGF (Epi-Prolif/Diff) polyclonal-Semiquan; CD105 monoclonal-Quan-MVD/FFPETS	NA;20X	VEGF Control[b] OSMF[a] OSMFWT-ED[a1] OSMFMLD[a2] OSMFMOD[a3] OSMFSEVD[a4] Up-regulation in VEGF expressions in both proliferative and differentiative layers of epithelium through the progression of dysplasia was noted. CD105 Control[b] OSMF[a] OSMFWT-ED[a1] OSMFMLD[a2] OSMFMOD[a3] OSMFSEVD[a4] The number of CD105 positive blood vessels and their major axis also showed significant increase from non-dysplasia	a1-a2=0.001 a2-a3=0.001 a3-a4<0.001 a1-a2<0.001 a3-a4<0.001	This result shows that increase in neo-angiogenic attributes of OSMF with increase in dysplastic grades indicated elucidatory potential of molecular expression features in assessment of malignant potentiality in oral submucous fibrosis.

								toward higher grades of dysplasia.		
13.	Anura A et al[32],2016/India	Case-control	68	OSMF 58 OSFWT OSFWD	10 NOM	CD105 Monoclonal/ VEGFRII polyclonal- digital quantification (positive vessel density/vessel count); VEGF polyclonal, - Quantifying Features (Intensity of Expression) Int – 10% - VEGF Int – 25% - VEGF Int – 50% - VEGF Int – 75% - VEGF Int – 90% - VEGF Quantifying Features (Extent of Expression) Cytoplasm Fraction of Expression (fr-VEGF) Initiation of Expression (IE – VEGF) Expression Thickness Fraction (ET – VEGF) Nuclear	Epithelium (Cytoplasm and nucleus) 200X; images were grabbed digitally by CCD camera (AxioCam MRC, Carl Zeiss, Oberkochen, Germany) at 1388 X1040 pixels Localization and Segmentation of Nuclei for IHC Quantification	G1 – NOM vs. OSFWT G2 – NOM vs. OSFWD G3 – OSFWT vs. OSFWD GI G2 G3 CD105-VC Inc Inc Inc CD105-VD Inc Inc Inc VEGFRII-VC Dec Inc Inc VEGFRII-VD Dec Inc Inc VEGF GI G2 G3 Fr - Inc Inc Inc IE – Inc Dec Dec ET –Dec Inc Inc Int – 10% - Nsc Nsc Dec Int – 25% - Nsc Nsc Dec Int – 50% - Nsc Nsc Dec Int – 75% - Nsc Dec Dec Int – 90% - Nsc Dec Dec		This study assessment of molecular expression proposed that VEGF for risk-stratification and VEGFRII and CD105 for prognosis of precancer into oral cancer.
14.	Lin Y et al[33], 2023/China	Case-control	40	OSMF 30 10 Early 10Moderately advanced 10 Advanced (Pindborg and Sirsat 1966 grading criteria)	10 NOM	VEGF/Qual/FFPETS	NA	VEGF Control Mainly expressed in basal cells, and a small amount of VEGF was expressed in vascular endothelial cells in the submucosa Early stage VEGF expressed more in the basal layer and submucosa than that in normal tissues. Early stage to advanced stage, VEGF level showed a decreasing trend.		This result revealed that angiogenesis plays role in pathogenesis of OSMF. Due to the synergistic effect between Pi3k/Akt pathway and VEGF on OSF lesions and fibrosis process, targeted Pi3k/Akt pathway regulation can induce VEGF expression and improve ischemia, ultimately treating OSMF.
15.	Das RK et al[34], 2010/India	Case-control	53	45 OSMF 15 OSMFWT-ED 30 OSMFW-ED OSFWMLD 13 OSFWMOD 11 OSFWSEVD 6	8 NOM	CD105/ Qual/ FFPETS	X10	CD105 OSFWT Faintly[a] OSFWMLD Remarkable[a1] OSFWMOD Remarkable[a2] OSFWSEV Maximum presence[a3] Control Absent[b]	b<a<a1<a2<a3	This result shows that malignant potential of this precancerous condition is likely to be correlated with an increase in p63 and CD105 expression and a concomitant loss of membranous E-cadherin. This may lead to marker identification through greater validation.
16.	Bavle RM et al[35],2020/India	Cross-sectional	36	OSMF 36 5 Early 23 Moderate	NA	CD31/monoclonal/FFPETS/quan-MVD/qual-predominant pattern of blood vessel	10X	MVD[A] Early 9.75±3.30[a] Moderate 12.04±3.77[b]	A=0.54	This result shows that increased expression of CD31 in cases of OSMF can be considered as

				8 Advanced (Khanna JN and Andrade NN 1995 grading system)		(diameter) -N/C/D		Advanced 12.00±2.20[c] Pattern of Blood vessel[B] Qual N C D Early 1 3 1[a] Moderate 12 5 6[b] Advanced 0 2 6[c]	B=0.02	definitive quantitative markers in the prediction of the malignant transformation of OSMF.
17.	S Desai R et al[39], 2012/India	Case-control	40	OSMF 30	10 NOM	VEGF (Cyt exprs-basal epith cells&fibroblast)/Semiquan/ FFPETS	NA	VEGF OSMF[a] 18 Mild 17 Mod 1 Control[b] 0 There was no statistically significant difference observed between the disease stages[c] and staining intensity of VEGF[d].	a>b=<0.05 c-d>0.05	This result suggesting that upregulation of VEGF may play an important role in tumor progression during malignant transformation of atrophic epithelium in OSF.
18.	Desai RS et al[40],2010/India	Case-control	40	OSMF 30 Clinical staging stage 1 >35mm stage 2 30-35mm stage 3 20-30mm stage 4 <20mm (Lai DR et al 1995 grading criteria)	10 NOM	CD34 monoclonal/Quan/ mean vascular density (MVD'), mean vascular luminal diameter (MVLD) and mean vascular area percentage (MVAP)/ FFPETS	3 hotspot fields, 40X	MVD[a] stage2 8.15±2.85 stage 3 7.18±4.74 stage 4 9.8±5.78 control 7.69±2.35 MVLD[b] stage2 150.22±67.77 stage 3 130.98±53.92 stage 4 127.16±50.08 control 105.72±34.35 MVAP[c] stage 2 3.21±1.03 stage 3 2.62±1.66 stage 4 2.46±1.52 control 2.06±1.03 Juxta epithelial loss of CD34-positive stromal cells in OSMF.	a-0.54 b-0.48 c-0.64	This result challenges the conventionally believed concept that epithelial atrophy in OSF is due to lack of perfusion, caused by decreased vascularity of subjacent connective tissue stroma. Characteristic pattern of juxtaepithelial loss of CD34-positive stromal cells in OSMF deserves further attention.
19.	Pammar C et al[41],2018/India	Case-control	45	OSMF 30 Clinical staging stage 1 >35mm stage 2 30-35mm stage 3 20-30mm stage 4 <20mm (Lai DR et al 1995 grading criteria)	15 NOM	CD34,CD105/quan-MVD/FFPETS	3 hotspots, 40X	MVD CD34 Control 19.63 OSMF 6.84 CD105 Control 3.25 OSMF 2.39 CD34 & CD105 with clinical staging CD34 CD105 Stage II 11.5±3.84. 2.3±0.84 Stage III 12.7±6. 1.7±0.50 Stage I & Stage IV CD34 & CD105 with histological grading CD34 CD105	 0.001 0.016 >0.05	This result shows that role of CD34 in determining the premalignant nature of OSF could not be ascertained, since all endothelial cells were positive for CD34, whereas CD105 appeared to be more specific as it is associated with hypoxia-induced angiogenesis which is occurring in OSF due to hyalinization suggesting, CD105 to be more specific marker to determine neoangiogenesis in OSF. Thus, further follow-up study of the cases positive for CD105 is required to determine the true nature of angiogenesis in OSF patients.

								Early 12.1±5.21 2.5±0.88 Mod Adv 11.6±4.39 2.2±0.77 Very early & Advanced	0.005 0.001 >0.05	
20.	Sabarinath B et al[42],2011/ India	Case-control	40	OSMF 30 Very early Early 9 Moderately 14 Advanced 7 (Pindborg and Sirsat 1966 grading criteria)	10 NOM	FFPETS/anti-factor VIII related von Willebrand factor/monoclonal/quan-MVD	40X	MVD VEOSMF 260.88[a1] EOSMF 272.00[a2] MADOSMF 283.42[a3] Control 80.40[b] A positive correlation in VEOSMF, EOSMF, MADOSMF and control between MCD and MVD.	a-b<0.05 a1-a2>0.05 a1-a3>0.05 a2-a3>0.05 a3-<0.01 a1,a2,b>0.01	This result demonstrates increase in MVD and MCD and reveals their role in the pathogenesis of OSMF, a lesion characterized by progressive fibrosis in early stages and failure of degradation or remodeling in the advanced stages.
21.	Sharma E et al[43],2019/India	Case-control	40	OSMF 30 10 Early 10Moderately advanced 10 Advanced (Pindborg and Sirsat 1966 grading criteria)	10 NOM	VEGF(Epi)-SemiQuan; CD34 monoclonal-quan / FFPETS	5 consecutives field, X40	VEGF Control 0.70 ± 0.63[b] OSMF 3.66 ± 2.22[a] Group I 4.33 ± 2.20[a1] Group II 3.75 ± 2.21[a2] Group III 2.89 ± 2.24[a3] MVD Control 3.84 ± 0.56[b] OSMF 12.53 ± 4.52[a] Group I 15.44 ± 4.13[a1] Group II 11.92 ± 2.78[a2] Group III 10.22 ± 5.03[a3] Correlation between CD34 and VEGF expressions was found to be statistically significant.	a-b< 0.001 a1-a2< 0.001 a2-a3< 0.007 a-b< 0.001 a1-b< 0.001 a2-b< 0.001 a3-b-0.002	This study shows that as the disease progresses, there is an increased production of the extracellular matrix component (collagen I and II and fibronectin) and results in fibrosis. Subsequently, it leads to the reduction in the level of corium vascularity and results in hypoxia which ultimately causes reduction and constriction of the vascular channels. This sequence of events alerts us to the relevance of early disease diagnosis and management in an irreversible pathology such as OSMF.
22.	Sharada P et al[44],2018/India	Case-control	20	10 OSMF	10 NOM	VEGF monoclonal/ Semiquan/FFPETS	5 selected field; NA	VEGF Basilar cells[A] 1+ 2+ Control 2.00±2.58 0.00 OSMF 20.00±25.82 33.33±66.14 Parabasilar cells[B] 1+ 2+ Control 2.00±2.58 0.00 OSMF 10.00±21.08 15.00±47.43 Superficial and corneal cells[C] OSMF 0 Control 0	A<0.05 B<0.05	This result demonstrates that angiogenesis does play a vital role in malignant transformation of OSMF.

(OSMF: oral submucous fibrosis, OSCC: oral squamous cell carcinoma, WDSCC: well differentiated squamous cell carcinoma, MDSCC: moderatley differentiated squamous cell carcinoma, PDSCC: poorly differentiated squamous cell carcinoma, NOM: normal oral mucosa, H&E: hematoxylin and eosin, Quan: Quantitative, Qual: qualitative, Semiquan: semiquantitative, FFPETS: formalin fixed paraffin embedded tissue section, NA: not available, OSMFW: ED-oral submucous fibrosis with epithelial dysplasia, OSMFWT: ED-oral submucous fibrosis without epithelial dysplasia, OSFWMLD: oral submucous fibrosis mild epithelial dysplasia, OSFWMOD: oral submucous fibrosis moderate epithelial dysplasia, OSFWSEVD: oral submucous fibrosis severe epithelial dysplasia, MVD: mean vascular density, MBVA: mean blood vessel area, MBVD: mean blood vessel diameter, MBVP: mean blood vessel perimeter, MVLD: mean vascular luminal diameter, OSMF-M: oral submucous fibrosis with malignant change, VEGF: vascular endothelial growth factor, N: normal, C: constricted, D: dilated, VEOSMF: very early oral submucous fibrosis, EOSMF: early oral submucous fibrosis, MAOSMF: moderately advanced oral submucous fibrosis, OSMF-MI: oral submucous fibrosis with micro invasion, Mod Adv: moderately advanced, Adv: advanced, LRED: low risk epithelial dysplasia, HRED: high risk epithelial dysplasia, Inc: increase, Dec: decrease, Nsc: no significant change)

Supplementary Table 4. Summarizes the haematoxylin and eosin assessment of angiogenic activity in oral submucous fibrosis for the entailed studies

S. No	Authors, year/ Country	Normal Oral Mucosa	OSMF/OSMF WT-ED	Very early Stage of OSMF	Early Stage of OSMF	Moderately Advanced Stage of OSMF	Advanced Stage of OSMF	OSMF-WED	OSCC with OSMF	OSCC
1.	Rajendran R et al[13],2005/India	MVD' more or less same	MVD' more or less same	MVPA↓* MVLD↓*	MVPA↑* MVLD↑*	MVPA↑* MVLD↑*	MVPA↑* MVLD↑*			
2.	Garg N et al[14], 2014/India	MBVA↑ MBVP↑ MBVD↑		MBVA↓ MBVP↓ MBVD↓	MBVA↑ MBVP↑ MBVD↑	MBVA↓ MBVP↓ MBVD↓	MBVA↓ MBVP↓ MBVD↓			
3.	Singh M et al[16], 2010/India			MVD' ↑ MVA ↓ MVLD ↓	MVD'↓ MVA ↑ MVLD↑#	MVD'↓ MVA ↓ MVLD↓	MVD'↓ MVA ↓ MVLD↓#			
4.	Sarode SC et al[17],2021/India								Conspicuous large dilated vascular spaces	
5.	Pal M et al[18],2020/India	MVA↑*	MVA↓*					MVA↑*		
6.	Debnath S et a1[19],2013/India			MVD' ↑* MVA↓* MVLD↓*	MVD'↓* MVA↑* MVLD↑#*	MVD'↓* MVA ↓* MVLD↓*	MVD'↓* MVA ↓* MVLD↓#*			
7.	Kapoor R et al[20],2022/India	MVD'↓	MVD'↑					MVD' Mild ED ↓ Mod ED ↑ Sev ED ↑		
8.	Murgod VV et al[21],2014/India	MVD'↓* MVA↓* MVPA↓* MVLD↓*	MVD' ↑* MVA↑* MVPA↑* MVLD↑		MVD' ↑* MVA↑* MVPA↑* MVLD↑*		MVD'↓* MVA↓* MVPA↓* MVLD↓*			MVD ↑* MVA↑* MVPA↑* MVLD↑*
9.	Sirsat SM et al[22],1967/India	N 10 N/D 0 D 2 D/C 1 N/C 1 C 1		N0 N/D0 D4 D/C0 N/C0 C0	N9 N/D1 D54 D/C0 N/C0 C0 MVLD-Dilatation#	N0 N/D6 D13 D/C22 N/C6 C6	N0 N/D0 D1 D/C6 N/C1 C1 MVLD-Narrowing#			

(OSMF: oral submucous fibrosis, OSMFWT: ED-oral submucous fibrosis without-epithelial dysplasia, OSMF-WED: oral submucous fibrosis with epithelial dysplasia, OSCC: oral squamous cell carcinoma, QD: quantity density, MVLD: mean vascular luminal diameter, MVQ: microvessel quantity, MVA: microvessel area, AD: area density, MVD: mean vascular density, MVAP: mean vascular area percentage, Mild ED: mild epithelial dysplasia, Mod ED: moderate epithelial dysplasia, Sev ED: severe epithelial dysplasia, N: normal, N/D: normal/dilated, D: dilated, D/C: dilated/constricted, N/C: normal/constricted, C: constricted)
*Statistically significant, #maximum.

Supplementary Table 5. Summarizes the immunohistochemical assessment of angiogenic activity in oral submucous fibrosis for the entailed studies

S. No	Authors, year/ Country	NOM	OSMF/ OSMF WT-ED	Clinical staging of OSMF				Histopath Grading of OSMF							OSMF-WED					OSMF with OSCC					OSCC				
				S1	S2	S3	S4								WHO classification			WHO Binary Grading/												
								E	M	A	VE	E	MA	A	Mild	Mod	Sev	LRED	HRED	W	G	S	L	S	W	G	S	L	S
CD31- MVD																													
1	Bavle RM et al[35], 2020/India							↓* (A.E) LD - C*	↑* (H/ D.E)	↑* (H/ D.E) LD-D*																			
Factor-VIII- MVD																													
2	Thakkannavar SS et al[10], 2019/India											↑*		↓*															
3	Gupta S et al[29], 2022/ India		↓										↓*	↑*						↑*									
4	Sabarinath B et al[42],2011/ India	↓*									↑	↑↑	↑↑↑																
CD34- MVD																													
5	Pandiar D et al[9], 2014/India	↑*										↓*	↓↓*	↓↓*	↑*					↑↑*									
6	Tekade SA et al[11],2017/ India	↓*						↑* TVA MVA	↓↓* TVA MVA	↓↓* TVA MVA																			
7	Madhavan Nirmal R et al[12], 2016/India	↑*	↓*					↓*	↓↓*	↓↓*					↑*					↑↑*									

8	Sheelam S et al[30], 2018/India	↓*	↓*																										
9	Desai RS et al[40] /2010/ India	↓			↑ LD↑ PA↑	↓ LD↓ PA↓	↑ LD↓ PA↓																						
10	Pammar C et al[41]/ 2018/India	↑	↓		↓*	↑*						↑*	↓*																
11	Sharma E et al[43], 2019/India	↓*	↑*									↑*	↓*	↓*															
CD105 MVD																													
12	Hande AH et al[24], 2022/India																		↓*	↓*	↓*	↓*	↓*	↑*	↑*	↑*	↑*	↑*	
13	Gadbail AR et al[25],2019/ India	↓															↑*	↑↑*						↑*					
14	Gadbail AR et al[26],2017/ India	↓															↑*	↑↑*											
15	Gadbail AR et al[27],2018/ India	↓															↑*	↑↑*											
16	Gadbail AR et al[28],2020/ India																		↓*					↑*					
17	Anura et al[31],2014/ India	0	↓*												↑*	↑*	↑↑*												
18	Anura et al[32],2016/ India	↓	↓*												↑*	↑*	↑↑*												

19	Das RK et al[34], 2010/ India	0	Faint												↑	↑	↑↑											
20	Pammar C et al[41], 2018/India	↑	↓		↓*	↑*						↑*	↓*															
VEGF-Staining intensity/positivity																												
21	Madhavan Nirmal R et al[12], 2016/India	↓	↓*			↑	↑	↑							↑*					↑*								
22	Sheelam S et al[30], 2018/India	↓*	↑*																									
23	Anura et al [31],2014/ India	↓	↓*												↑*	↑*	↑↑*											
24	Anura et al[32],2016/ India	↓	↑*												↑*	↑*	↑↑*											
25	Lin Y et al[33],2023/ China	↓								↑	↓	↓																
26	Desai RS et al[39], 2012/India	↓*	↑*						NS	NS	NS	NS																
27	Sharma E et al[43], 2019/India	↓*	↑*							↑*	↓*	↓*																
28	Sharada P et al[44], 2018/ India	↓*	↑*																									

(A.E: atrophic epithelium, H/D.E: hyperplastic/dysplastic epithelium, LD: luminal diameter, PA: percentage area, C: constriction, D: dilatation, TVA: total vascular area, MVA: mean vascular area, W: OSMF with OSCC cases without grade, G: grade of differentiation, S: staging, L: lymphnode metastasis, S: survival, NS: non-significant, OSMF: oral submucous fibrosis, OSMFWT-ED: oral submucous fibrosis without-epithelial dysplasia, OSMF-WED: oral submucous fibrosis with epithelial dysplasia, OSCC: oral squamous cell carcinoma, QD: quantity density, MVLD: mean vascular luminal diameter, MVQ: microvessel quantity, MVA: microvessel area, AD: area density, MVD: mean vascular density, MVAP: mean vascular area percentage, Mild ED: mild epithelial dysplasia, Mod ED: moderate epithelial dysplasia, Sev ED: severe epithelial dysplasia, N: normal, N/D: normal/dilated, D: dilated, D/C: dilated/constricted, N/C: normal/constricted, C: constricted, VE: very early, E: early, M: moderately advanced, A: advanced, LRED: low risk epithelial dysplasia, HRED: high risk epithelial dysplasia, Mod: moderate, Sev: severe)
*Statistically significant, #maximum.