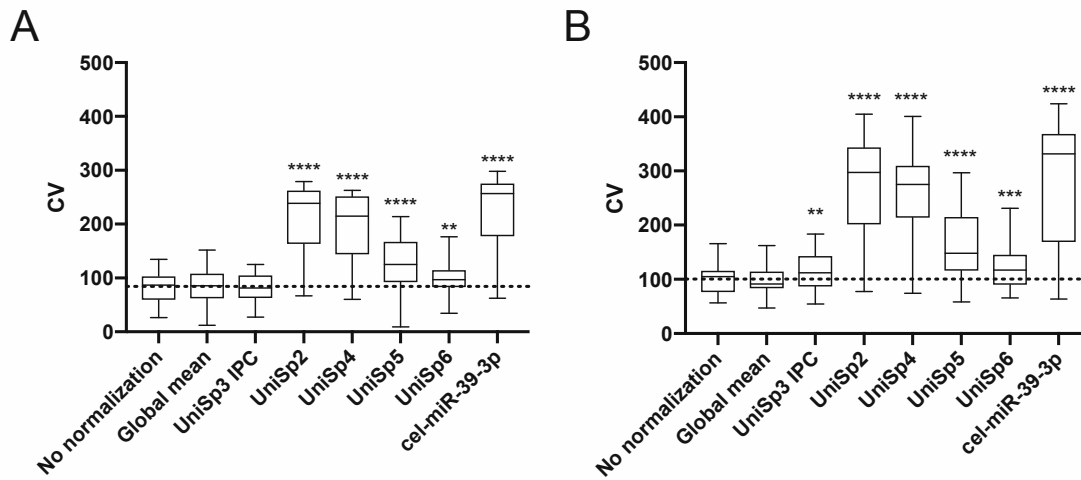


Supplementary information

Supplemental Table 1. Primers used for single qPCR assays.

miRNA	Cat No	Assay ID	System	Company
hsa-miR-20a-5p	YP00204292		miRCURY LNA	Qiagen
hsa-miR-23b-3p	YP00204790		miRCURY LNA	Qiagen
hsa-miR-142-3p	YP00204291		miRCURY LNA	Qiagen
hsa-miR-185-5p	YP00206037		miRCURY LNA	Qiagen
hsa-miR-199a-5p	YP00204494		miRCURY LNA	Qiagen
hsa-miR-223-3p	YP00205986		miRCURY LNA	Qiagen
hsa-miR-326	YP00204512		miRCURY LNA	Qiagen
hsa-miR-362-5p	YP00204618		miRCURY LNA	Qiagen
hsa-miR-662	YP00204180		miRCURY LNA	Qiagen
cel-miR-39-3p	YP00203952		miRCURY LNA	Qiagen
UniSp6	YP00203954		miRCURY LNA	Qiagen
cel-miR-55-3p	A25576	478295_mir	TaqMan	Thermo Fisher
hsa-miR-223-3p	A25576	477983_mir	TaqMan	Thermo Fisher
hsa-miR-326	A25576	478027_mir	TaqMan	Thermo Fisher
hsa-miR-362-5p	A25576	478059_mir	TaqMan	Thermo Fisher
hsa-miR-662	A25576	479145_mir	TaqMan	Thermo Fisher



Supplemental Figure 1. Contribution of different normalization methods on sample variance. Of 33 miRNAs, the coefficient of variation (CV) in no normalized (“No normalization”) and normalized qPCR values from control samples only (n = 10) (A) or all 20 samples (B) was calculated. Box whisker plots are shown, representing median values with minimum and maximum values. The dotted line indicates the mean CV of all miRNAs without normalization (non-normalized values: 84.1% in B and 103.1% in C). Compared to non-normalized values, most normalization methods significantly increased CV (**P < 0.01, *** P < 0.001, **** P < 0.0001), as determined by paired t-tests.

Supplemental Table 2. miRNAs regularly expressed in the vitreous of control and PDR patients. miRNAs found to be expressed in $\geq 70\%$ of all samples in one condition were considered to be regularly expressed and are marked in **bold** (miRNAs regularly expressed in Control: 24; miRNAs regularly expressed in PDR: 26).

miRNA	Control	PDR
hsa-miR-142-3p	30%	80%
hsa-miR-149-5p	70%	60%
hsa-miR-185-5p	20%	70%
hsa-miR-197-3p	60%	70%
hsa-miR-199a-5p	70%	20%
hsa-miR-204-5p	70%	70%
hsa-miR-20a-5p	10%	70%
hsa-miR-21-5p	80%	80%
hsa-miR-222-3p	90%	80%
hsa-miR-223-3p	50%	80%
hsa-miR-23a-3p	50%	80%
hsa-miR-23b-3p	20%	70%
hsa-miR-320a	70%	80%
hsa-miR-324-3p	90%	90%
hsa-miR-326	100%	60%
hsa-miR-329-3p	100%	100%
hsa-miR-345-5p	90%	90%
hsa-miR-361-5p	100%	100%
hsa-miR-362-5p	100%	100%
hsa-miR-373-3p	70%	70%
hsa-miR-376c-3p	80%	50%
hsa-miR-454-3p	80%	80%
hsa-miR-491-5p	80%	100%
hsa-miR-502-5p	80%	80%
hsa-miR-509-3p	80%	60%
hsa-miR-595	70%	70%
hsa-miR-598-3p	100%	100%
hsa-miR-615-3p	80%	70%
hsa-miR-662	0%	70%
hsa-miR-663a	90%	90%
hsa-miR-760	70%	100%
hsa-miR-765	60%	50%
hsa-miR-877-5p	80%	60%

Supplemental Table 3. miRNA levels in vitreous of control (CON) and PDR patients in the three cohorts.

miRNA	CON (N = 10)				PDR (N = 10)				Fold change	P-value
	% of samples	median	1st Q	3rd Q	% of samples	median	1st Q	3rd Q		
hsa-let-7a-5p	20 %	12.27	6.93	17.61	60%	21.89	14.86	30.34	1.78	0.0549
hsa-let-7b-5p	60 %	13.45	6.19	17.21	60%	22.32	9.74	42.82	1.66	0.5580
hsa-let-7c-5p	60 %	5.89	3.27	7.87	60%	10.26	5.55	15.39	1.74	0.7846
hsa-miR-101-3p	-	-	-	-	30%	10.99	6.74	32.55	-	0.0779
hsa-miR-124-3p	30 %	12.12	7.28	13.30	40%	6.14	2.82	175.36	0.51	0.7562
hsa-miR-125a-5p	40 %	22.67	18.65	35.55	10%	1.82	1.82	1.82	0.08	0.1012
hsa-miR-125b-5p	20 %	34.11	25.49	42.73	50%	36.88	36.33	63.75	1.08	0.1692
hsa-miR-128-3p	40 %	1.28	1.19	1.77	20%	4.04	2.77	5.32	3.15	0.5447
hsa-miR-130a-3p	10 %	2.92	2.92	2.92	40%	9.31	4.61	14.49	3.19	0.1236
hsa-miR-140-3p	60 %	19.60	2.67	54.24	50%	17.62	2.65	49.42	0.90	0.7815
hsa-miR-142-3p	30 %	7.79	4.90	15.71	80%	19.01	16.25	32.62	2.44	0.0125
hsa-miR-144-3p	20 %	15.72	14.31	17.13	40%	3.10	1.70	7.60	0.20	0.5447
hsa-miR-149-5p	70 %	22.53	1.38	36.87	60%	13.10	1.75	56.56	0.58	0.9078
hsa-miR-15a-5p	10 %	31.73	31.73	31.73	40%	18.59	11.32	30.92	0.59	0.1799
hsa-miR-16-5p	40 %	26.26	17.80	41.70	50%	24.70	12.15	104.81	0.94	0.6490
hsa-miR-185-5p	20 %	46.64	38.74	54.53	70%	62.17	21.90	99.20	1.33	0.0349
hsa-miR-187-5p	50 %	10.70	1.89	16.94	20%	6.16	4.28	8.05	0.58	0.1692
hsa-miR-191-5p	50 %	13.24	3.25	19.88	30%	1.87	1.40	3.75	0.14	0.2323
hsa-miR-193a-5p	-	-	-	-	40%	3.16	1.76	4.56	-	0.0350
hsa-miR-197-3p	60 %	3.28	2.22	22.81	70%	3.09	2.46	20.04	0.94	0.6710
hsa-miR-199a-5p	70 %	17.42	3.10	18.49	20%	0.97	0.96	0.98	0.06	0.0091
hsa-miR-202-3p	40 %	4.57	2.42	11.15	-	-	-	-	-	0.0350
hsa-miR-204-5p	70 %	29.96	27.38	56.09	70%	29.53	7.34	49.33	0.99	0.5918
hsa-miR-205-5p	60 %	14.04	6.98	20.50	40%	20.44	16.73	21.30	1.46	0.5447
hsa-miR-206	20 %	4.65	3.69	5.60	50%	1.29	0.97	5.68	0.28	0.2675
hsa-miR-20a-5p	10 %	3.93	3.93	3.93	70%	2.66	1.77	30.18	0.68	0.0133
hsa-miR-210-3p	10 %	1.58	1.58	1.58	50%	20.02	4.85	43.31	12.65	0.0403
hsa-miR-211-5p	40 %	44.88	18.31	68.41	50%	18.79	12.53	21.23	0.42	0.9670
hsa-miR-21-5p	80 %	12.67	7.81	23.71	80%	125.91	35.35	275.89	9.93	0.0878
hsa-miR-222-3p	90 %	7.14	1.76	24.47	80%	4.52	1.93	8.97	0.63	0.4720
hsa-miR-223-3p	50 %	34.58	31.45	35.64	80%	61.42	33.18	87.75	1.78	0.0407
hsa-miR-23a-3p	50 %	15.44	13.17	16.12	80%	17.38	14.44	34.99	1.13	0.0822
hsa-miR-23b-3p	20 %	2.47	1.99	2.95	70%	9.18	7.83	13.25	3.71	0.0116
hsa-miR-24-3p	20 %	36.06	24.55	47.58	60%	26.68	22.86	30.75	0.74	0.0962
hsa-miR-25-3p	-	-	-	-	40%	15.74	10.98	21.09	-	0.0350
hsa-miR-27b-3p	30 %	4.26	3.53	10.05	50%	1.04	1.01	1.18	0.24	0.6697
hsa-miR-30c-5p	10 %	16.58	16.58	16.58	40%	24.63	16.70	29.89	1.49	0.1236
hsa-miR-31-5p	20 %	4.92	3.92	5.93	50%	2.62	2.32	2.76	0.53	0.3517
hsa-miR-320a	70 %	15.44	7.28	20.25	80%	31.31	15.32	61.75	2.03	0.1375
hsa-miR-324-3p	90 %	4.64	4.57	21.25	90%	4.45	2.88	14.98	0.96	0.5452
hsa-miR-326	100 %	14.31	9.22	45.24	60%	7.92	3.00	25.14	0.55	0.0168
hsa-miR-329-3p	100 %	12.88	9.71	21.47	100%	7.06	3.40	10.46	0.55	0.0892
hsa-miR-345-5p	90 %	18.52	6.20	23.05	90%	15.53	8.13	32.42	0.84	0.5452
hsa-miR-361-5p	100 %	257.65	48.89	513.75	100%	77.26	25.16	210.62	0.30	0.3930
hsa-miR-362-5p	100 %	3.89	2.59	5.42	100%	7.50	4.26	11.62	1.93	0.0433
hsa-miR-373-3p	70 %	71.44	36.54	80.34	70%	10.40	7.01	43.29	0.15	0.4436
hsa-miR-373-5p	10 %	2.36	2.36	2.36	40%	2.57	1.43	4.73	1.09	0.1497
hsa-miR-376c-3p	80 %	3.49	1.95	4.91	50%	2.22	2.03	3.66	0.64	0.1320
hsa-miR-412-3p	40 %	3.78	1.42	7.00	40%	1.12	1.07	1.63	0.30	0.6389
hsa-miR-451a	20 %	18.30	17.16	19.44	40%	61.56	45.51	252.99	3.36	0.2083
hsa-miR-454-3p	80 %	34.02	14.82	53.33	80%	13.61	1.55	30.38	0.40	0.3057
hsa-miR-485-3p	30 %	32.39	19.47	48.32	20%	33.42	28.91	37.92	1.03	0.6548
hsa-miR-491-5p	80 %	72.58	25.13	81.12	100%	8.84	4.60	20.11	0.12	0.3445
hsa-miR-495-3p	30 %	1.04	1.03	1.16	50%	1.20	1.10	1.52	1.15	0.3059
hsa-miR-502-5p	80 %	8.28	3.05	27.98	80%	7.33	3.87	10.26	0.89	0.7906
hsa-miR-509-3p	80 %	42.97	25.63	104.57	60%	28.42	24.46	61.60	0.66	0.3010
hsa-miR-519d-3p	20 %	5.97	4.94	6.99	-	-	-	-	-	0.1681
hsa-miR-523-3p	40 %	45.07	29.00	60.12	40%	10.74	5.41	17.78	0.24	0.5792
hsa-miR-524-5p	50 %	24.95	4.22	32.73	30%	30.65	17.42	35.82	1.23	0.4426
hsa-miR-542-5p	60 %	46.90	28.21	76.21	40%	39.67	19.12	55.40	0.85	0.3530
hsa-miR-545-3p	60 %	17.43	12.25	29.74	60%	5.67	3.27	18.55	0.33	0.4581
hsa-miR-595	70 %	5.89	3.66	10.72	70%	3.16	2.32	4.20	0.54	0.4905
hsa-miR-598-3p	100 %	23.19	16.93	40.95	100%	36.82	28.11	71.80	1.59	0.2799
hsa-miR-615-3p	80 %	4.11	2.36	8.03	70%	2.95	2.42	3.29	0.72	0.3811
hsa-miR-642a-5p	40 %	9.72	6.82	11.44	20%	2.83	2.11	3.56	0.29	0.2440
hsa-miR-662	-	-	-	-	70%	7.23	2.49	12.94	-	0.0022
hsa-miR-663a	90 %	11.50	2.19	26.36	90%	3.40	1.69	24.03	0.30	1.0000
hsa-miR-671-5p	40 %	3.94	1.61	6.27	20%	12.05	6.80	17.31	3.06	0.4283
hsa-miR-760	70 %	30.77	23.29	46.57	100%	20.01	11.54	35.58	0.65	0.7910

hsa-miR-765	60 %	21.12	11.75	24.24	50%	24.74	22.18	26.89	1.17	0.9684
hsa-miR-766-3p	60 %	3.27	1.61	4.79	60%	2.91	2.22	4.71	0.89	0.9689
hsa-miR-877-5p	80 %	33.10	15.39	49.95	60%	32.95	7.78	47.20	1.00	0.3383
hsa-miR-92a-3p	-	-	-	-	30%	48.53	28.24	184.72	-	0.0779
hsa-miR-934	40 %	7.22	2.84	17.83	30%	3.97	3.67	13.81	0.55	0.7562
hsa-miR-940	40 %	6.42	5.02	12.23	50%	6.21	1.68	15.60	0.97	0.8361
hsa-miR-99a-3p	40 %	20.62	11.65	27.91	10%	42.11	42.11	42.11	2.04	0.2143

Confirmation cohort

miRNA	CON (N = 17)			PDR (N = 11)			Fold change	P-value
	median	1st Q	3rd Q	median	1st Q	3rd Q		
hsa-miR-142-3p	22.62	19.64	28.75	83.36	32.89	129.16	3.69	0.0004
hsa-miR-185-5p	55.34	48.24	62.44	428.90	79.43	1300.37	7.75	0.0004
hsa-miR-199a-5p	5.82	4.38	6.71	6.64	2.58	7.45	1.14	0.2088
hsa-miR-20a-5p	21.95	12.61	26.59	63.33	27.30	1318.33	2.89	0.001
hsa-miR-223-3p	146.16	44.28	368.09	92.59	47.02	621.54	0.63	0.3138
hsa-miR-23b-3p	9.17	7.06	15.46	44.91	21.71	63.47	4.90	0.0034
hsa-miR-326	204.35	103.23	305.47	96.66	36.48	538.56	0.47	0.0013
hsa-miR-362-5p	21.52	17.12	29.92	27.92	24.14	40.24	1.30	0.0487

Anti-VEGF cohort

miRNA	Treated (N = 17)			Untreated (N = 16)			Fold change	P-value
	median	1st Q	3rd Q	median	1st Q	3rd Q		
hsa-miR-142-3p	60.17	30.72	145.52	58.23	25.49	115.36	0.97	0.1697
hsa-miR-185-5p	40.66	33.83	112.58	119.64	51.05	1133.17	2.94	0.3772
hsa-miR-20a-5p	39.77	23.36	126.84	56.96	26.77	167.04	1.43	0.2433
hsa-miR-23b-3p	12.16	9.52	20.63	40.12	17.22	62.17	3.30	0.0203
hsa-miR-326	223.57	0.89	1309.85	395.81	89.83	1722.49	1.77	0.4218
hsa-miR-362-5p	36.91	28.82	183.22	31.63	24.55	55.09	0.86	0.1646

Data are presented in absolute amounts with 1st and 3rd quartile values.

The Mann-Whitney U test was used to assess statistical differences between groups.