Table S1. Primers for RT-qPCR.

Symbol (ID)	Type	Sequence (5'-3')	Product size
Actb (11461)	Forward	B662302 (Sangon, Shanghai, China)	174bp
	Reverse	B662302 (Sangon, Shanghai, China)	
Mif (17319)	Forward	GCATCGGCAAGATCGGTGGTG	130bp
	Reverse	ACGTTGGCAGCGTTCATGTCG	
Mdk (17242)	Forward	GCTTCTTCCTTCTCGCCCTTCTTG	84bp
	Reverse	CGCTGCCCTTCTTCACCTTCTC	
Lgals9 (16859)	Forward	CTACTCCTGGAATCCCTCCTGTGG	137bp
	Reverse	CTACTCCTGGAATCCCTCCTGTGG	

Table S2A. The concordance between clinical and histological grouping

	Clinical inactive	Clinical active
Histological:		
Inactive	101	69
Active	13	72
Accuracy	0.678	
Cohen's Kappa	0.379	
Binomial test	P<0.001	

Table S2B. The concordance between clinical and endoscopic grouping

	Clinical inactive	Clinical active
Endoscopic:		
Inactive	177	36
Active	155	225
Accuracy	0.678	
Cohen's Kappa	0.377	
Binomial test	P<0.001	

Table S2C. The concordance between histological and endoscopic grouping

	Histological inactive	Histological active
Endoscopic:		
Inactive	56	8
Active	114	77
Accuracy	0.522	
Cohen's Kappa	0.179	
Binomial test	P = 1.000	

Table S2D. The concordance between clinical and CDRG-based grouping

	Clinical inactive	Clinical active
CDRG-based:		
Inactive	273	102
Active	60	161
Accuracy	0.728	
Cohen's Kappa	0.439	
Binomial test	P<0.001	

Table S2E. The concordance between histological and CDRG-based grouping

	Histological inactive	Histological active
CDRG-based:		
Inactive	128	18
Active	42	67
Accuracy	0.765	
Cohen's Kappa	0.506	
Binomial test	P<0.001	

Table S2F. The concordance between endoscopic and CDRG-based grouping

	Endoscopic inactive	Endoscopic active
CDRG-based:		
Inactive	169	204
Active	44	176
Accuracy	0.581	
Cohen's Kappa	0.220	
Binomial test	P = 0.999	

Table S3A. The concordance between the inconsistences of histological grouping to clinical grouping and CDRG-based grouping to clinical grouping

	Histological consistent	Histological inconsistent
CDRG-based:		
Consistent	144	31
Inconsistent	29	51
Accuracy	0.765	
Cohen's Kappa	0.457	
Binomial test	P = 0.002	

Table S3B. The concordance between the inconsistences of endoscopic grouping to clinical grouping and CDRG-based grouping to clinical grouping

	Endoscopic consistent	Endoscopic inconsistent
CDRG-based clustering:		
Consistent	293	139
Inconsistent	109	52
Accuracy	0.582	
Cohen's Kappa	0.001	
Binomial test	P = 1.000	

Table S3C. The concordance between the inconsistences of histological grouping to clinical grouping and endoscopic grouping to clinical grouping

	Histological consistent	Histological inconsistent
Endoscopic:		
Consistent	112	61
Inconsistent	61	21
Accuracy	0.522	
Cohen's Kappa	-0.097	
Binomial test	P = 1.000	

Table S3D. The concordance between the clinical and endoscopic grouping in CDRG-consistent samples

	Clinical inactive	Clinical active
Endoscopic:		
Inactive	149	16
Active	123	144
Accuracy	0.678	
Cohen's Kappa	0.394	
Binomial test	P = 0.020	

Table S3E. The concordance between the histological and endoscopic grouping in CDRG-consistent samples

	Histological inactive	Histological active
Endoscopic:		
Inactive	41	6
Active	68	60
Accuracy	0.577	
Cohen's Kappa	0.241	
Binomial test	P = 0.907	

Table S3F. The concordance between the clinical and endoscopic grouping in CDRG-inconsistent samples

	Clinical inactive	Clinical active
Endoscopic:		
Inactive	28	20
Active	32	81
Accuracy	0.677	
Cohen's Kappa	0.280	
Binomial test	P = 0.110	

Table S3G. The concordance between the histological and endoscopic grouping in

CDRG-inconsistent samples

	Histological inactive	Histological active
Endoscopic:		
Inactive	15	2
Active	46	17
Accuracy	0.400	
Cohen’s Kappa	0.078	
Binomial test	P = 1.000	

Table S4A. The concordance between clinical and DEG-based grouping

	Clinical inactive	Clinical active
DEG-based:		
Inactive	312	129
Active	15	114
Accuracy	0.747	
Cohen's Kappa	0.450	
Binomial test	P<0.001	

Table S4B. The concordance between histological and DEG-based grouping

	Histological inactive	Histological active
DEG-based:		
Inactive	140	25
Active	19	56
Accuracy	0.817	
Cohen's Kappa	0.582	
Binomial test	P<0.001	

Table S4C. The concordance between endoscopic and DEG-based grouping

	Endoscopic inactive	Endoscopic active
DEG-based:		
Inactive	196	243
Active	13	115
Accuracy	0.549	
Cohen's Kappa	0.211	
Binomial test	P = 1.000	

Table S4D. The concordance between DEG-based and CDRG-based grouping

	DEG-based inactive	DEG-based active
CDRG-based:		
Inactive	354	3
Active	87	126

Accuracy	0.842
Cohen's Kappa	0.634
Binomial test	P < 0.001

Table S4E. The concordance between the inconsistences of DEG-based grouping to clinical grouping and CDRG-based grouping to clinical grouping

	DEG-based consistent	DEG-based inconsistent
CDRG-based:		
Consistent	378	42
Inconsistent	48	102
Accuracy	0.842	
Cohen's Kappa	0.588	
Binomial test	P < 0.001	

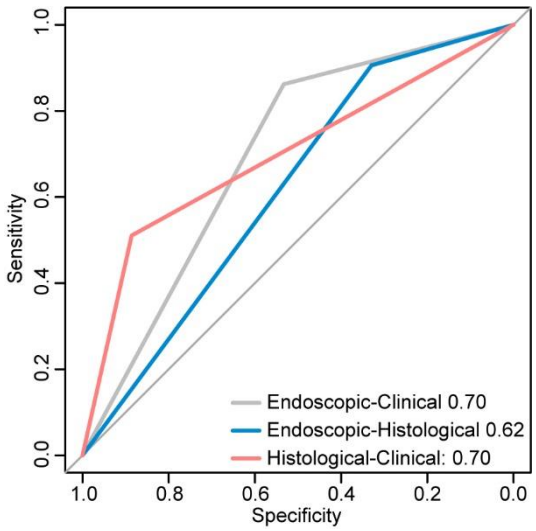

Figure S1. Predictive values of histological grouping to clinical grouping and endoscopic grouping to clinical and histological grouping.

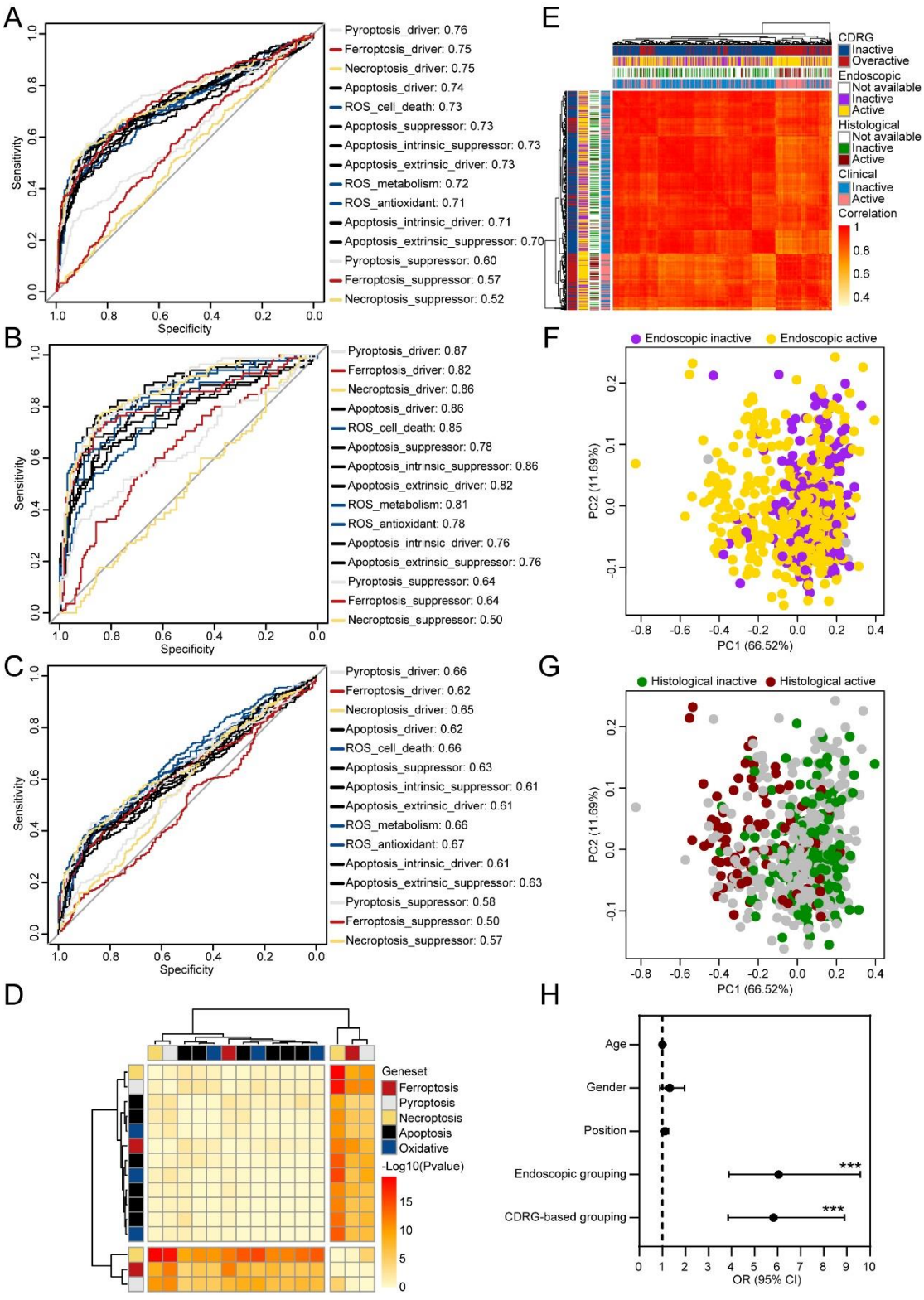

Figure S2. Predictive values CDRGs and CDRG-based grouping. (A-C) Predictive values of 15 CDRGs to clinical (A), histological (B), and endoscopic (C) grouping. (D) Unsupervised hierarchical clustering on the comparisons of AUCs in the prediction of 15 CDRGs to clinical grouping, with -log10 transformed P value, (E) Unsupervised hierarchical clustering on the

sample-sample correlations based on 15 CDRGs. (F-G) Distribution of samples in CDRG-based PCA grouped by endoscopic (F) or histological (G) grouping. (H) Odds ratio of age, gender, biopsy position, endoscopic grouping, and CDRG-based clustering in multivariable logistic regression analysis were showed in forest plot.

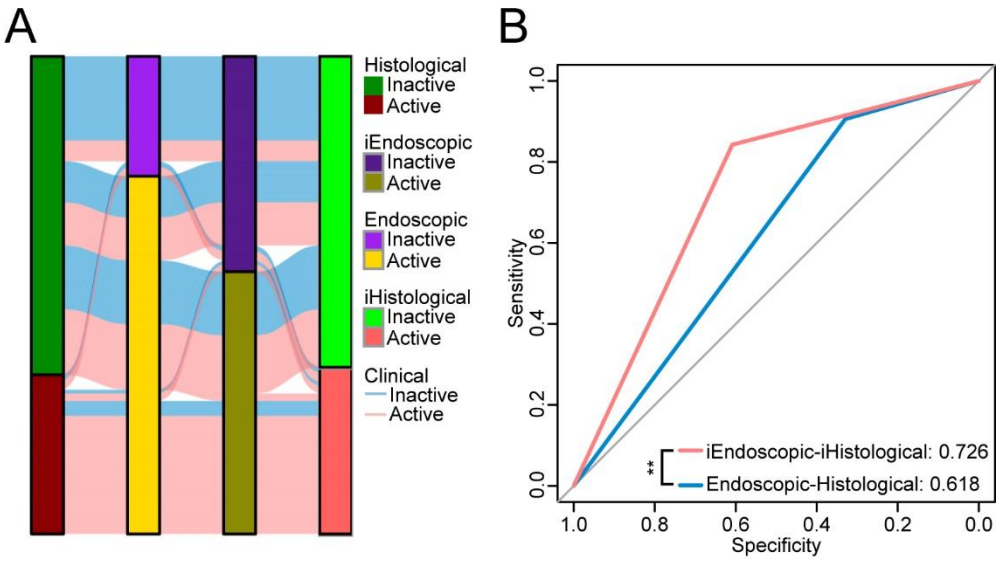

Figure S3. Improved concordance between histological and endoscopic grouping after integration with CDRG-based grouping. (A) Concordance between histological grouping, iMES grouping, endoscopic grouping and iNancy grouping. (B) Predictive values of iMES grouping on iNancy grouping, compared with endoscopic grouping to histological grouping.

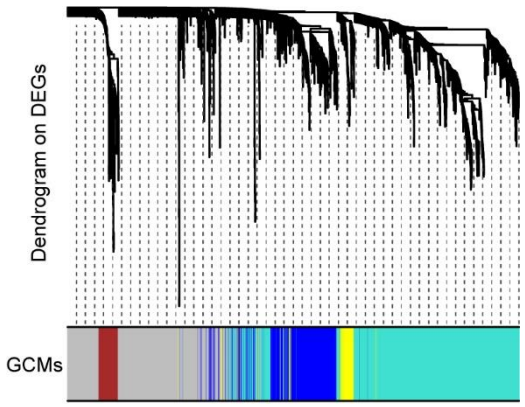

Figure S4. Dendrogram of differentially expressed genes with corresponding gene co-expression modules in weighted gene co-expression network analysis.

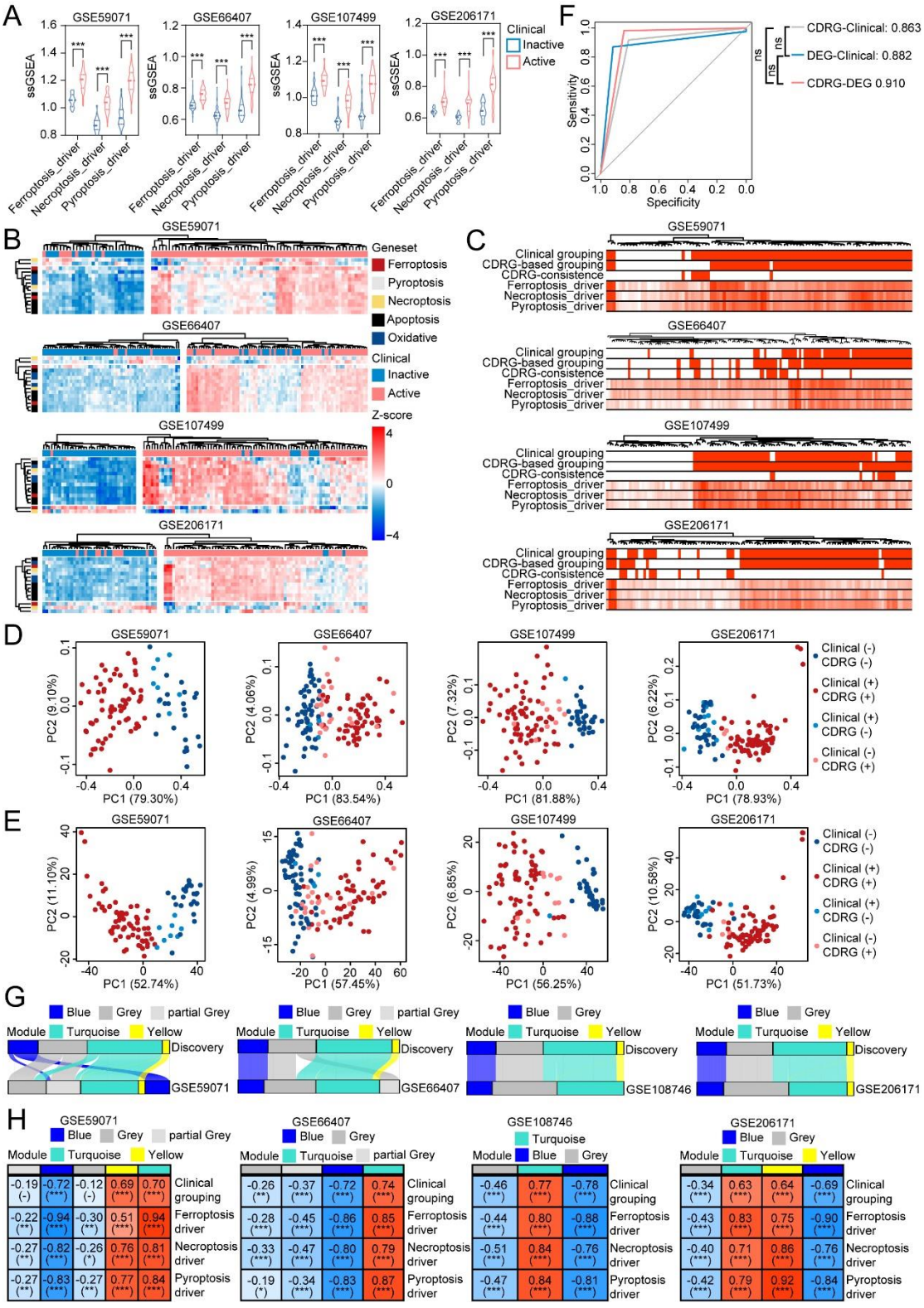

Figure S5. Intrinsic association between cell death related genesets and altered gene-expression patterns was reproduced in multiple validation cohorts of UC with large sample size. (A) Median, upper/lower quartiles, and upper/lower limits of the CDRGs' activities created using ssGSEA in 4 validation cohorts. (B) Unsupervised hierarchical clustering based on CDRGs in 4 validation cohorts. (C) Unsupervised hierarchical clustering based on DEGs of 4 confident GCMs in 4 validation cohorts, with annotation of clinic, CDRG-based

clustering, CDRG-inconsistence to clinic, and 3 representative CDRGs. (D) Distribution of samples grouped by clinic and CDRG-based clustering in PCA based on CDRGs in 4 validation cohorts. (E) Distribution of samples grouped by clinic and CDRG-based clustering in PCA based on DEGs with genes of brown GCM excluded. (F) Predictive value of CDRG-based clustering and DEG-based clustering to clinic, and of CDRG-based clustering to DEG-based clustering in samples of 4 validation cohorts. (G) Concordance between 4 confident GCMs of discovery cohort and GCMs detected in 4 validation cohorts. (H) Correlations between the GCMs detected in 4 validation cohorts and clinic and 3 representative CDRGs. ns, $P > 0.05$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

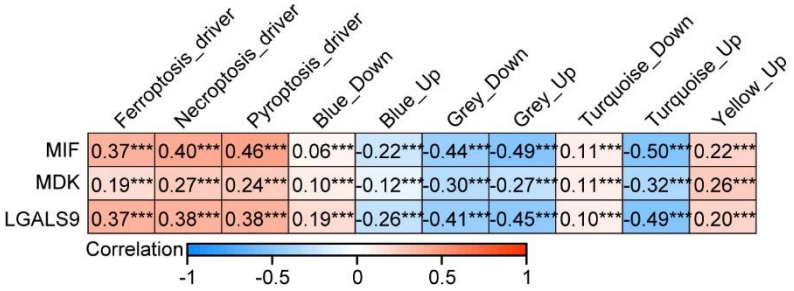

Figure S6. MIF, MDK, and LGALS9 correlated with 3 representative CDRGs and split GCMs in epithelial cells from scRNA-seq.