The High Expression of Minichromosome Maintenance Complex Component 5 Is an Adverse Prognostic Factor in Lung Adenocarcinoma

Man Sun, Tao Wang, Yonglin Zhu, Yanmei Zhang, Lichao Zhu, and Xiaoxiao Li

Department of Geriatrics, The Second Affiliated Hospital of Zhengzhou University, No. 2 Jingba Road, Zhengzhou 450000, China

Correspondence should be addressed to Man Sun; mansun0520@sina.com

Received 13 December 2021; Revised 21 February 2022; Accepted 7 March 2022; Published 20 March 2022

Academic Editor: Xiangqian Guo

Copyright © 2022 Man Sun et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Minichromosome maintenance (MCM) genes are crucial for genomic DNA replication and are important biomarkers in tumor biology. In this study, we aimed to identify the diagnostic, therapeutic, and prognostic value of the MCM2–10 genes in patients with lung cancer.

Methods. We examined the expression levels, gene networks, and protein networks of lung cancer using data from the ONCOMINE, GeneMANIA, and STRING databases. We conducted a functional enrichment analysis of MCM2–10 using the clusterProfiler package using TCGA data. The correlation between the MCM2–10 expression and lung cancer prognosis was evaluated using Cox regression analysis. The influence of clinical variables on overall survival (OS) was evaluated using univariate and multivariate analyses. The TIMER database was used to evaluate the correlation between tumor infiltrating levels and lung cancer. Kaplan–Meier Plotter pan-cancer RNA sequencing was used to estimate the correlation between the MCM5 expression and OS in different immune cell subgroups in patients with lung adenocarcinoma (LUAD). Finally, the 1-, 3-, and 5-year predictions of LUAD were performed using nomogram and calibration analysis.

Results. The expression of MCM2, 3, 4, 5, 6, 7, 8, and 10 in lung cancer was higher than that for normal samples. The MCM5 expression was associated with poor OS in patients with LUAD, and prognosis was related to TNM stage, smoking status, and pathological stage. The MCM5 expression is correlated with immune infiltration in LUAD and may affect prognosis due to immune infiltration. Conclusion. MCM5 may serve as a molecular biomarker for LUAD prognosis.

1. Introduction

Lung cancer is the leading cause of cancer-related morbidity and mortality worldwide [1]. Numerous studies have evaluated therapeutic approaches for reducing mortality rates in patients with lung adenocarcinoma (LUAD) [2]; however, the 5-year survival rate of patients with lung cancer from 2009 to 2015 was only 19% [3]. Further studies are required to identify accurate and promising prognostic biomarkers and efficient therapeutic targets to enhance survival rates in patients with lung cancer and to guide customized treatments [4].

The minichromosome maintenance (MCM) gene family plays key roles in DNA replication and cell cycle progression [5]. DNA replication errors can lead to tumorigenesis [6]. MCM family proteins are involved in the occurrence and development of cancer [7]. Indeed, several studies have shown that MCM proteins are highly expressed in various cancers, including pancreatic ductal adenocarcinoma [8], hepatocellular carcinoma [9], and colorectal cancer [10] and can be used as molecular markers for diagnosis and prognosis. Teresita et al. suggested that the progression of precancerous lung disease to carcinoma in situ is enhanced in MCM2-overexpressing cells [11]. MCM3 is involved in
the carcinogenesis of multiple cancers [12] and is associated with the development of LUAD [13]. Yi et al. identified MCM4 as a potential lung cancer driver gene and demonstrated that MCM4 upregulation is associated with poorer survival in patients with lung cancer [14]. MCM6 levels are higher in primary lung tumors with both FHIT and p53 inactivation [15]. MCM7 is involved in tumor formation, progression, malignant transformation, and prognosis [16] and can be used as a potential biomarker for the poor prognosis of non-small-cell lung cancer [17]. MCM9 is an outlier within the MCM family, containing a long C-terminal extension comprising 42% of the total length, but with no known functional components and high predicted disorder [18]. MCM10 acts as an oncogene that promotes the progression of hepatocellular carcinoma [19]. However, a correlation between the MCM2–10 gene expression and immune infiltration in lung cancer has rarely been reported.

Accordingly, in this study, bioinformatic methods were used to analyze online public databases to assess the expression of MCM2–10 genes in patients with lung cancer and the relationship between this expression and tumor prognosis. Our findings may contribute to the screening, diagnosis, treatment, and prognosis of patients with lung cancer.

2. Materials and Methods

2.1. ONCOMINE and the Cancer Genome Atlas (TCGA). ONCOMINE (http://www.oncomine.org/) is a tumor microarray database with functions for differential gene expression analysis, correlation analysis between gene expression and clinical features, prognostic analysis, and multigene coexpression analysis [20, 21]. The differential expression of MCM2–10 in lung cancer was measured using Student’s t-test ($p < 0.01$, fold change: 1.5, gene rank: 10%, data type: mRNA). We used paired sample t-test analysis TCGA (https://portal.gdc.cancer.gov/) LUADLUSC (lung cancer) [22] in the project level 3 HTSeq-RNAseq FPKM format data to assess target genes in lung cancer and normal tissues ($ns, \ p \geq 0.05; \ *p < 0.05; \ **p < 0.01; \ ***p < 0.001$).

2.2. Networks of MCM2–10 Interacting Genes and Proteins. GeneMANIA (http://www.genemania.org) is useful for predicting the function of MCM2–10. The STRING database
The protein–protein interactions of MCM2–10 (version 11.5; https://string-db.org/) was used to determine data to explore genetic alterations in MCM2 investigated Pan Lung Cancer (TCGA, Nat Genet 2016) analyzing multidimensional cancer genomics data [25]. We from more than 5,000 tumor samples from 20 cancer studies mics Portal (cBioPortal; http://cbioportal.org) utilizes data 2.4. cBioPortal for Cancer Genomics. The cBio Cancer Genomics Portal (cBioPortal; http://cbioportal.org) utilizes data from more than 5,000 tumor samples from 20 cancer studies to provide a web resource for exploring, visualizing, and analyzing multidimensional cancer genomics data [25]. We investigated Pan Lung Cancer (TCGA, Nat Genet 2016) [26] data to explore genetic alterations in MCM2–10.

2.3. Functional Enrichment and KEGG Pathway Analysis of MCM2–10. Gene Ontology (GO) functional annotation was performed using biological processes (BP), cellular components (CC), and molecular functions (MF). The Kyoto Encyclopedia of Genes and Genomes (KEGG) (https://www.kegg.jp/kegg/) pathway is useful for understanding molecular interactions, reactions, genetic information processing, environmental information processing, cellular processes, and human diseases. The following R packages were used: clusterProfiler package (version 3.14.3) for GO and KEGG enrichment analyses and ggplot2 package (version 3.3.3) for visualization [24].

2.4. cBioPortal for Cancer Genomics. The cBio Cancer Genomics Portal (cBioPortal; http://cbioportal.org) utilizes data from more than 5,000 tumor samples from 20 cancer studies to provide a web resource for exploring, visualizing, and analyzing multidimensional cancer genomics data [25]. We investigated Pan Lung Cancer (TCGA, Nat Genet 2016) [26] data to explore genetic alterations in MCM2–10.

2.5. The Prognostic Value of MCMs in Patients with Lung Cancer. The correlation between the MCM2–10 expression and lung cancer prognosis was evaluated by Cox regression analysis of TCGA data [27], the survminer package (version 0.4.9) for visualization, and the survival package (version 3.2-10) for statistical analysis of survival data. The influence of the clinical variables on overall survival (OS) was evaluated using univariate and multivariate analyses. Kaplan–Meier Plotter pan-cancer RNA-sequencing (RNA-seq) [28] was used to estimate the correlation between the MCM5 expression and OS in different immune cell subgroups of patients with LUAD.

2.6. Intergroup Comparison of the MCM5 Gene Expression and Tumor Clinical Variables. The Wilcoxon rank-sum test was used to compare the tumor and normal lung tissue groups. The Kruskal–Wallis test was used for intergroup comparison of TNM stage, pathological stage, sex, age, smoking status, primary therapy outcome, and overall

### Table 1: The mRNA expression of MCM2-10 was significantly expressed in lung cancer (ONCOMINE).

| Type of lung cancer vs. normal | Fold change | p value | t-test | Ref |
|-------------------------------|-------------|---------|--------|-----|
| Lung adenocarcinoma           | 1.993       | 7.61E-17| 10.52  | Landi et al. [37] |
| Lung adenocarcinoma           | 3.251       | 3.46E-13| 9.295  | Hou et al. [33]  |
| Squamous cell lung carcinoma  | 6.171       | 1.99E-05| 12.132 | Wachi et al. [39]|
| Squamous cell lung carcinoma  | 2.204       | 1.13E-11| 8.803  | Talbot et al. [51]|
| Lung adenocarcinoma           | 1.617       | 4.13E-16| 9.920  | Selamat et al. [34]|
| Lung adenocarcinoma           | 1.047       | 3.39E-07| 5.093  | TCGA     |
| Squamous cell lung carcinoma  | 1.653       | 1.33E-10| 7.742  | Talbot et al. [51]|
| Squamous cell lung carcinoma  | 2.387       | 8.85E-05| 4.773  | Garber et al. [36]|
| Lung adenocarcinoma           | 2.403       | 8.50E-19| 11.190 | Landi et al. [37]|
| Lung adenocarcinoma           | 2.649       | 7.09E-10| 8.123  | Su et al. [35]   |
| Lung adenocarcinoma           | 1.668       | 6.17E-12| 8.670  | Okayama et al. [38]|
| Lung adenocarcinoma           | 1.100       | 3.68E-16| 8.605  | TCGA     |
| Squamous cell lung carcinoma  | 3.108       | 4.84E-07| 8.298  | Garber et al. [36]|
| Squamous cell lung carcinoma  | 1.101       | 1.12E-22| 10.441 | TCGA     |
| Lung adenocarcinoma           | 1.810       | 4.58E-06| 5.433  | Garber et al. [36]|
| Lung adenocarcinoma           | 1.367       | 4.16E-06| 5.442  | Beer et al. [52] |
| Squamous cell lung carcinoma  | 4.682       | 7.91E-07| 5.941  | Bhattacharjee et al. [40]|
| Squamous cell lung carcinoma  | 1.072       | 7.43E-15| 8.033  | TCGA     |
| Lung adenocarcinoma           | 1.797       | 2.63E-12| 8.130  | Selamat et al. [34]|
| Squamous cell lung carcinoma  | 2.650       | 6.05E-17| 12.633 | Hou et al. [33]  |
| Squamous cell lung carcinoma  | 1.023       | 5.34E-05| 3.920  | TCGA     |
| Lung adenocarcinoma           | 1.628       | 2.08E-10| 7.057  | Landi et al. [37]|
| Squamous cell lung carcinoma  | 2.691       | 5.94E-15| 13.573 | Hou et al. [33]  |
| Lung adenocarcinoma           | 1.322       | 6.39E-12| 8.202  | Selamat et al. [34]|
| Lung adenocarcinoma           | 1.431       | 3.51E-08| 6.860  | Okayama et al. [38]|
| Squamous cell lung carcinoma  | 3.587       | 6.27E-12| 10.719 | Hou et al. [33]  |
| NA                            |             |         |        |      |
| Lung adenocarcinoma           | 1.733       | 5.36E-14| 9.601  | Selamat et al. [34]|
| Squamous cell lung carcinoma  | 4.099       | 4.06E-16| 14.598 | Hou et al. [33]  |
Figure 2: Continued.
Plasmacytoid DCs, T cells, T helper cells, T central memory, (NK) CD56 bright cells, NK CD56 dim cells, NK cells, DCs, macrophages, mast cells, neutrophils, natural killer (NK) CD56 bright cells, NK CD56 dim cells, NK cells, plasmacytoid DCs, T cells, T helper cells, T central memory, T effector memory, T follicular helper, T gamma delta (Tgd), Th1 cells, Th17 cells, Th2 cells, and regulatory T (Treg) cells.

2.7. Tumor Immune Estimation Resource (TIMER). TIMER (https://cistrome.shinyapps.io/timer/) was used to evaluate the correlation between tumor-infiltrating levels in lung cancer and alterations of different somatic copy numbers in MCM5 [29, 30]. The correlation between the MCM5 expression and six immune infiltrates (B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells [DCs]) was estimated using the TIMER algorithm. The sGSVA package (version 1.34.0) [31] and Spearman correlation analysis were applied to correlate MCM5 and B cells, CD8+ T cells, cytotoxic cells, DC, eosinophils, immature DCs, macrophages, mast cells, neutrophils, natural killer (NK) CD56 bright cells, NK CD56 dim cells, NK cells, plasmacytoid DCs, T cells, T helper cells, T central memory, T effector memory, T follicular helper, T gamma delta (Tgd), Th1 cells, Th17 cells, Th2 cells, and regulatory T (Treg) cells [32].

3. Results

3.1. The Overexpression of Different MCM2–10 Genes in Lung Cancer. The transcriptional expression of MCM2–10 genes in lung cancer and normal samples was investigated using the ONCOMINE database (http://www.oncomine.org/); Figure 1, Table 1). In the data investigated, MCM genes showed overall overexpression in lung cancer. The fold change varied, with the highest fold change of 3.251 for MCM2 [33], 1.617 for MCM3 [34], 2.649 for MCM4 [35], 1.810 for MCM5 [36], 1.797 for MCM6 [34], 1.628 for MCM7 [37], 1.431 for MCM8 [38], 1.733 for MCM10 [34] in LUAD, and 6.171 for MCM2 [39], 2.387 for MCM3 [36], 3.108 for MCM4 [36], 4.682 for MCM5 [40], 2.650 for MCM6 [33], 2.691 for MCM7 [33], 3.587 for MCM8 [33], and 4.099 for MCM10 [33] in lung squamous cell carcinoma (LUSC). A t-test of paired samples showed that the expression of MCM2, 3, 4, 5, 6, 7, 8, and 10 in lung cancer was higher than the average level of normal, and the difference was statistically significant (p < 0.001; Figure 2).

3.2. Functional Enrichment of MCM2–10 in Patients with Lung Cancer. Gene-gene interaction (Figure 3(a)) and protein-protein networks (Figure 3(b)) of MCM2–10 were constructed. The functional enrichment of 30 molecules obtained from the protein-protein network was predicted using the clusterProfiler package. GO terms were analyzed according to BP, MF, and CC (Figure 3(c) and Supplemental Table 1). The BP associated with MCM2–10 included DNA-dependent DNA replication, DNA replication, and DNA replication initiation. The MF were associated with DNA replication origin binding, DNA helicase activity, 3′-5′-DNA helicase activity, catalytic activity, acting on DNA, and helicase activity. The CC were associated with MCM complex, nuclear chromosome, telomeric region, chromosome, telomeric region, chromosomal region, and nuclear replication fork. In the KEGG analysis, five pathways were associated with MCM2–10, and the cell cycle pathway accounted for the highest proportion. The cBioPortal online tool was then used to evaluate the frequency of MCM2–10 alteration in lung cancer. In total, 1144 samples from TCGA were analyzed, and the percentage of genetic alterations in MCM2–10 for lung cancer varied from 1.1% to 5% (Figure 3(d)).

3.3. Clinical Value of MCM5 in Lung Cancer. We explored the prognostic value of MCM genes in the OS of patients with lung cancer. The mRNA expression of MCM5 (p = 0.008) was closely linked to worse OS in patients with lung cancer (Figure 4(d), Table 2). MCM5 was highly expressed in patients with lung cancer and was closely related to TNM stage, pathological stage, sex, age, smoking status, primary therapy outcomes, and OS, PFI, and DSS events (Figure 5 and Supplemental Table 2). Furthermore,
Figure 3: The gene-gene and protein-protein interaction network, functional enrichment, and genomic alterations of MCM2-10. (a) The gene-gene network associated with the MCM2-10 (GeneMANIA). (b) The protein-protein network of MCM2-10 (STRING). (c) The GO and KEGG enrichment of MCM2-10. (d) Alteration frequency of MCM2-10 in lung cancer patients (cBioPortal). GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes (KEGG).
Figure 4: Correlation analysis of the abnormal MCM2-10 expression and overall survival in patients with lung cancer. (d) The mRNA expression of MCM5 was significantly associated with worse OS in patients with lung cancer, HR = 1.31 (1.07–1.59), p = 0.008. Red represents high expression, and blue represents low expression.
we explored the correlation between MCM5 expression and clinicopathological parameters on OS in patients with lung cancer, and poor OS was associated with LUAD, TNM stage, smoking status, and pathological stage (Figures 6(a) and 6(c)–6(g)).

3.4. Correlation between the MCM5 Expression and Immune Infiltration Level. The TIMER online tool was used to investigate the correlation between the MCM5 expression and immune cell infiltration in lung cancer. The somatic copy number alteration module showed that the arm-level gain of MCM5 was significantly associated with immune cell infiltration levels in LUAD and LUSC (Figure 7(a)). MCM5 was positively correlated with the infiltration levels of Th2, NK CD56dim, Tgd, and Treg cells in lung cancer (Figure 7(b)). The MCM5 expression was positively correlated with the infiltration levels of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs in LUAD (Figure 7(c)). MCM5 was positively correlated with infiltration levels of CD4+ T cells and DCs in LUSC (Figure 7(c)).

3.5. Prognostic Analysis of the MCM5 Expression Based on Immune Cells in LUAD Patients and Prognostic Predictive Model. The high MCM5 expression was closely related to LUAD prognosis and immune cell infiltration. We further explored whether the high MCM5 expression affected the prognosis because of immune infiltration. The Kaplan-Meier Plotter pan-cancer RNA-seq LUAD (n = 513) data were analyzed for the prognosis of enriched and decreased immune cells. Poor OS was seen in LUAD patients with the high MCM5 expression and enriched infiltration of basophils, B cells, CD4+ memory T cells, CD8+ T cells, eosinophils, macrophages, mesenchymal stem cells, natural killer T cells, Treg cells, and type 2 T-helper cells, and in LUAD patients with the high MCM5 expression and decreased infiltration of basophils, B cells, CD4+ memory T cells, eosinophils, mesenchymal stem cells, natural killer T cells, Treg cells, and type 1 T-helper cells. Enriched type 1 T-helper cells, decreased macrophages, and type 2 T-helper cells showed no significant correlation between the MCM5 expression and OS in patients with LUAD (Figure 8(a)). These findings reveal that MCM5 may affect the prognosis of patients with LUAD, in part due to immune infiltration. Finally, we used nomogram and calibration analysis to predict the 1-, 3-, and 5-year OS of patients with LUAD using clinically related factors such as age, smoking status, pathological stage, and primary therapy outcome (Figures 8(b) and 8(c)).

4. Discussion

Recent studies have suggested that dysregulation of MCMs leads to tumor initiation, progression, and chemoresistance via modulation of the cell cycle and DNA replication stress.
The expression of MCM5 Log2 (FPKM+1)

(a) Normal Tumor

(b) T stage

(c) N stage

(d) M stage

(e) Pathologic stage

(f) Gender

**Figure 5:** Continued.
Figure 5: The expression of MCM5 in different clinical features of lung cancer. MCM5 was highly expressed in lung cancer and closely related to TNM stage, pathologic stage, sex, age, smoker, OS event, PFI event, DSS event, and primary therapy outcome, ns, $p \geq 0.05$; $^* p < 0.05$; $^{**} p < 0.01$; $^{***} p < 0.001$. OS: overall survival; PFI: progression-free interval; DSS: disease-specific survival; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.
Survival probability

Overall survival

HR = 1.38 (1.13–1.69)

P = 0.002

0 50 100 150 200 250 100

Overall survival

HR = 1.31 (1.07–1.60)

P = 0.008

0 50 100 150 200 250 100

Survival probability

Time (Months)

LUAD

Pathologic stage: stage I & stage II & stage III & stage IV

Overall survival

HR = 1.38 (1.13–1.69)

P < 0.001

0 50 150 250 200 100

Time (Months)

Overall survival

HR = 1.86 (1.38–2.50)

P < 0.001

0 50 150 250 200 100

Time (Months)

Overall survival

HR = 0.86 (0.65–1.12)

P = 0.261

0 50 150 200 100

Time (Months)

Overall survival

HR = 1.38 (1.13–1.69)

P = 0.002

0 50 150 200 250 100

Time (Months)

Overall survival

HR = 1.30 (1.06–1.58)

P = 0.01

0 50 150 200 250 100

Time (Months)

Overall survival

HR = 1.27 (1.04–1.55)

P = 0.018

0 50 150 200 250 100

Time (Months)

Figure 6: Continued.
The MCM protein plays a key role in the proliferation and prognosis of lung cancer [16]. Bioinformatic analysis was used to detect mRNA expression, prognostic value, genetic mutations, functional enrichment, protein-protein network, and immune infiltration of MCMs in patients with lung cancer.

MCM2 plays a role in the proliferation, circulation, and migration of lung cancer cells [42]. MCM3 regulates cell proliferation by binding to cyclin D1 [43]. Mutations in MCM4 disrupt the functions of MCM2-7, resulting in genomic instability and cancer progression [44]. MCM5 is an important DNA replication initiation factor and is strongly downregulated following the overexpression of the long noncoding RNA CARMN [45]. MCM6, MCM7, and MCM8 collaborate with other MCM family members to promote cancer cell proliferation through cell cycle and DNA replication [46, 47]. The MCM9 protein is involved in the unwinding activity [48]. MCM10 mediates DNA replication by collaborating with other cell-dividing cyclins [49]. The BP and associated pathways of MCM2-10 were elucidated by GO and KEGG enrichment analyses, which are useful for investigating the pathological mechanisms of lung cancer. The BP associated with MCM2–10 includes DNA-dependent DNA replication, DNA replication, DNA replication initiation, G1/S transition of mitotic cell cycle, and cell cycle G1/S phase transition. The cell cycle and DNA replication pathways are associated with MCM2–10. MCM2-8 and MCM10 were highly expressed in paired lung cancer samples and may be involved in the development of lung cancer through the cell cycle and DNA replication.

Correlation analysis between the MCM2-10 expression and OS revealed that only MCM5 was closely related to poor OS in patients with lung cancer. The MCM5 gene affects the prognosis of LUAD by regulating BP and pathways, such as cell cycle and DNA replication [50]. In this study, MCM5 was highly expressed in tumors, which is related to TNM stage, pathological stage, sex, age, smoking status, prognostic events, and primary therapy outcomes. MCM5 was positively correlated with poor OS in patients with LUAD and was influenced by TNM stage, smoking status, age, and pathological stage. These results suggest that MCM5 is involved in the development of lung cancer, may be used as a molecular target for diagnosis and treatment, and is an independent prognostic marker of lung cancer. Furthermore, we revealed that the arm-level gain of MCM5 was significantly associated with immune cell infiltration levels in lung cancer. MCM5 positively correlated with B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs in LUAD. Enriched type 1 T-helper cells, decreased macrophages, and type 2 T-helper cells showed no significant correlation between the MCM5 expression and OS in patients with LUAD, whereas decreased type 1 T-helper cells, enriched macrophages, and type 2 T helper cells were related to the OS of patients with LUAD. MCM5 may partially influence the OS of patients with LUAD by immune cell infiltration. However, the exact role of MCM5 in the tumor immune microenvironment requires further investigation. Furthermore, we revealed that the arm-level gain of MCM5 was significantly associated with immune cell infiltration levels in lung cancer. MCM5 positively correlated with the infiltration levels of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and DCs, and partially influenced the OS of patients with LUAD by immune cell infiltration. Thus, MCM5 may serve as a molecular biomarker for immunotherapy. However, the exact role of MCM5 in the tumor immune microenvironment requires further exploration.

Our study had certain limitations. The data were collected online from open databases. In future studies, large clinical datasets are required to verify our findings, and the
Figure 7: Continued.
Figure 7: Correlations between the MCM5 expression and immune cells. (a) Correlation of tumor infiltrating levels in lung cancer and different somatic copy numbers’ alterations in the MCM5 expression. (b) Correlations between the MCM5 expression and 24 immune cells. (c) MCM5 was positively correlated with infiltration levels of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells in LUAD and positively correlated with CD4+ T cells and dendritic cells in LUSC.
role of MCM2–10 in the pathogenesis of lung cancer should be further explored.

5. Conclusions

Our findings demonstrated that MCM2-8 and 10 were highly expressed in lung cancer, and only MCM5 affected the prognosis of patients with lung cancer. The influence of MCM5 on the prognosis of lung cancer patients was related to LUAD, smoking, pathologic stage, and TNM stages. We further confirmed that the abnormal expression of MCM5 in LUAD was related to immune cell infiltration, and immune cell infiltration may contribute to the prognosis of LUAD partly. The above findings suggested that MCM5 can be used as a molecular marker for the prognosis of LUAD.

| Subgroups                          | Numbers | HR (95% CI)     | P-value |
|------------------------------------|---------|-----------------|---------|
| Basophils                          | 149     | 1.94 (1.14–3.32)| 0.013   |
| decreased                          | 352     | 2.13 (1.39–2.89)| 0.00015 |
| B-cells                            | 392     | 1.83 (1.3–2.58) | 0.00045 |
| enriched                           | 109     | 3.47 (1.97–6.11)| 4.9e-06 |
| CD4+ memory T-cells                | 352     | 2.1 (1.48–2.97) | 1.8e-05 |
| enriched                           | 149     | 2.22 (1.29–3.83)| 0.0032  |
| decreased                          | 275     | 2.27 (1.5–3.45) | 6.9e-05 |
| increased                          | 226     | 1.71 (1.08–2.7) | 0.021   |
| Eosinophils                        | 342     | 1.91 (1.31–2.79)| 0.00067 |
| decreased                          | 159     | 2.01 (1.25–3.23)| 0.0032  |
| Macrophages                        | 429     | 2.01 (1.46–2.77)| 1.2e-05 |
| decreased                          | 72      | 1.68 (0.73–3.87)| 0.22    |
| Mesenchymal stem cells             | 350     | 1.84 (1.31–2.58)| 0.00033 |
| decreased                          | 151     | 2.59 (1.44–4.66)| 0.0001  |
| Natural killer T-cells             | 219     | 1.73 (1.09–2.72)| 0.017   |
| enriched                           | 282     | 2.31 (1.57–3.4) | 1.3e-05 |
| decreased                          | 290     | 1.95 (1.32–2.88)| 0.00062 |
| increased                          | 211     | 2.54 (1.51–4.25)| 0.00025 |
| Type 1 T-helper cells              | 140     | 1.67 (0.98–2.86)| 0.057   |
| enriched                           | 361     | 2.12 (1.48–3.04)| 3.2e-05 |
| decreased                          | 289     | 1.83 (1.28–2.64)| 9e-09   |
| Type 2 T-helper cells              | 212     | 1.65 (0.99–2.76)| 0.053   |

**Figure 8:** Relationship between MCM5 and immune infiltration with overall survival (OS). (a) A forest plot shows the prognostic value of MCM5 expression according to different immune cell subgroups in LUAD patients. (b) Nomogram for predicting the probability of 1-, 3-, and 5-year OS for patients with LUAD. (c) Calibration plot of the nomogram for predicting the OS likelihood.
Data Availability

The data in this paper were mined from online public databases.

Conflicts of Interest

The authors claim that the research was conducted without any commercial or financial relationships that could be interpreted as potential conflicts of interest.

Acknowledgments

We would like to thank the ONCOMINE, cbioProteal, TCGA databases, GeneMANIA, STRING, and TIMER for availability of the data. This article was funded by the 2018 Henan Province Medical Science and Technology Program Joint Construction Project (no. 2018020165).

Supplementary Materials

Supplementary 1. C:\Users\86137\Desktop\supplemental Table 1.html.
Supplementary 2. C:\Users\86137\Desktop\supplemental Table 2.html.

References

[1] R. Wang, T. Yamada, K. Kita et al., “Transient igf-1r inhibition combined with osimertinib eradicates axl-low expressing egfr mutated lung cancer,” Nature Communications, vol. 11, no. 1, pp. 1–14, 2020.
[2] D. S. Ettinger, D. E. Wood, C. Aggarwal et al., “Nccn guidelines insights: Non-small cell lung cancer, version 1.2020,” Journal of the National Comprehensive Cancer Network, vol. 17, no. 12, pp. 1464–1479, 2019.
[3] R. L. Siegel, K. D. Miller, A. Goding Sauer et al., “Colorectal cancer statistics,” CA: a Cancer Journal for Clinicians, vol. 70, no. 3, pp. 145–164, 2020.
[4] A. Dherasi, Q. T. Huang, Y. Liao et al., “A seven-gene prognostic signature predicts overall survival of patients with lung adenocarcinoma (luad),” Cancer Cell International, vol. 21, no. 1, pp. 1–16, 2021.
[5] S. Li, Z. Jiang, Y. Li, and Y. Xu, “Prognostic significance of minichromosome maintenance mrna expression in human lung adenocarcinoma,” Oncology Reports, vol. 42, no. 6, pp. 2279–2292, 2019.
[6] L. Deng, R. A. Wu, R. Sonnville et al., “Mitotic cdk promotes replisome disassembly, fork breakage, and complex DNA rearrangements,” Molecular Cell, vol. 73, no. 5, pp. 915–929, 2019.
[7] B. Huang, M. Lin, L. Lu et al., “Identification of minichromosome maintenance 8 as a potential prognostic marker and its effects on proliferation and apoptosis in gastric cancer,” Journal of Cellular and Molecular Medicine, vol. 24, no. 24, pp. 14415–14425, 2020.
[8] X. Liao, C. Han, X. Wang et al., “Prognostic value of minichromosome maintenance mrna expression in early-stage pancreatic ductal adenocarcinoma patients after pancreaticoduodenectomy,” Cancer Management and Research, vol. 10, pp. 3255–3271, 2018.
[9] X. Liao, X. Liu, C. Yang et al., “Distinct diagnostic and prognostic values of minichromosome maintenance gene expression in patients with hepatocellular carcinoma,” Journal of Cancer, vol. 9, pp. 2357–2373, 2018.
[10] “Rna sequencing analysis of molecular basis of sodium butyrate-induced growth inhibition on colorectal cancer cell lines,” BioMed Research International, vol. 2019, 11 pages, 2019.
[11] T. Muñoz-Antonia, C. Muro-Cacho, S. Sharma, A. Cantor, and G. Bepler, “Expression of tgfbeta type-ii receptor in association with markers of proliferation and apoptosis in premalignant lung lesions,” Cancer: Interdisciplinary International Journal of the American Cancer Society, vol. 110, no. 7, pp. 1527–1531, 2007.
[12] S. A. Ha, S. M. Shin, H. Namkoong et al., “Cancer-associated expression of minichromosome maintenance 3 gene in several human cancers and its involvement in tumorigenesis,” Clinical Cancer Research, vol. 10, no. 24, pp. 8386–8395, 2004.
[13] H. Xu, J. Ma, J. Wu et al., “Gene expression profiling analysis of lung adenocarcinoma,” Brazilian Journal of Medical and Biological Research, vol. 49, 2016.
[14] J. Yi, X. Wei, X. Li, L. Wan, J. Dong, and R. Wang, “A genome-wide comprehensive analysis of alterations in driver genes in non-small-cell lung cancer,” Anti-Cancer Drugs, vol. 29, no. 1, pp. 10–18, 2018.
[15] F. Andriani, E. Roz, R. Caserini et al., “Inactivation of both fhit and p53 cooperate in deregulating proliferation-related pathways in lung cancer,” Journal of Thoracic Oncology, vol. 7, no. 4, pp. 631–642, 2012.
[16] S. Fujioka, K. Shomori, K. Nishihara et al., “Expression of minichromosome maintenance 7 (mcm7) in small lung adenocarcinomas (pt1): Prognostic implication,” Lung Cancer, vol. 65, no. 2, pp. 223–229, 2009.
[17] Y. Z. Liu, Y. Y. Jiang, J. J. Hao et al., “Prognostic significance of mcm7 expression in the bronchial brushings of patients with non-small cell lung cancer (nsclc),” Lung Cancer, vol. 77, no. 1, pp. 176–182, 2012.
[18] D. R. McKinsey, S. Gomathinayagam, W. C. Griffin et al., “Motifs of the c-terminal domain of mcm9 direct localization to sites of mitomycin-c damage for rad51 recruitment,” Journal of Biological Chemistry, vol. 296, article 100355, 2021.
[19] W. Yan, Y. Shen, and Q. Li, “Mcm10 acts as a potential prognostic biomarker and promotes cell proliferation in hepatocellular carcinoma: integrated bioinformatics analysis and experimental validation,” Cancer Management and Research, vol. 12, pp. 9609–9619, 2020.
[20] D. Rhodes, J. Yu, K. Shancer et al., “Oncomine: a cancer microarray database and integrated data-mining platform,” Neoplasia, vol. 6, no. 1, pp. 1–6, 2004.
[21] G. Ning, Y. L. Huang, L. M. Zhen et al., “Transcriptional expressions of chromobox 1/2/3/6/8 as independent indicators of survivability in hepatocellular carcinoma patients,” Aging, vol. 10, pp. 3450–3473, 2018.
[22] K. Tomczak, P. Czerwińska, and M. Witwerowicz, “The cancer genome atlas (tcga): an immeasurable source of knowledge,” Contemporary Oncology, vol. 19, no. 1A, pp. A68–A77, 2015.
[23] D. Szklarczyk, A. L. Gable, D. Lyon et al., “String v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental
datasets,” *Nucleic Acids Research*, vol. 47, no. D1, pp. D607– DD13, 2019.

[24] G. Yu, L. G. Wang, Y. Han, and Q. Y. He, “Clusterprofile: an r package for comparing biological themes among gene clusters,” *Omics: a Journal of Integrative Biology*, vol. 16, no. 5, pp. 284–287, 2012.

[25] J. Gao, B. A. Aksoy, U. Dogrusoz et al., “Integrative analysis of complex cancer genomics and clinical profiles using the cBioportal,” *Science Signaling*, vol. 6, no. 269, article pl1, 2013.

[26] J. D. Campbell, B. A. Aksoy, J. Kim et al., “Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas,” *Nature Genetics*, vol. 48, no. 6, pp. 607–616, 2016.

[27] J. Liu, S. Selamat, B. Chung, L. Girard et al., “Pan-cancer clinical data resource to drive high-quality survival outcome analytics,” *Cell*, vol. 173, no. 2, pp. 400–416, 2018.

[28] Á. Nagy, G. Munkácsy, and B. Gyorffy, “Pancancer survival analysis of cancer hallmark genes,” *Scientific Reports*, vol. 11, no. 1, pp. 1–10, 2021.

[29] T. Li, J. Fan, B. Wang et al., “Timerr: A web server for comprehensive analysis of tumor-infiltrating immune cells,” *Cancer Research*, vol. 77, no. 21, pp. e108–e110, 2017.

[30] B. Li, E. Severson, J. C. Pignon et al., “Comprehensive analyses of tumor immunity: implications for cancer immunotherapy,” *Genome Biology*, vol. 17, no. 1, pp. 1–16, 2016.

[31] S. Hänzelmann, R. Castelo, and J. Guinney, “Gsva: Gene set variation analysis for microarray and rna-seq data,” *BMC Bioinformatics*, vol. 14, no. 1, pp. 1–15, 2013.

[32] G. Bindea, B. Mlecnik, M. Tosolini et al., “Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer,” *Immunity*, vol. 39, no. 4, pp. 782–795, 2013.

[33] J. Hou, J. Aerts, B. Den Hamer et al., “Gene expression-based classification of non-small cell lung carcinomas and survival prediction,” *Plos One*, vol. 5, no. 4, article e10312, 2010.

[34] S. Selamat, B. Chung, L. Girard et al., “Genome-scale analysis of DNA methylation in lung adenocarcinoma and integration with mrna expression,” *Genome Research*, vol. 22, no. 7, pp. 1197–1211, 2012.

[35] L. J. Su, C. W. Chang, Y. C. Wu et al., “Selection of ddx5 as a novel internal control for q-rt-pcr from microarray data using a block bootstrap re-sampling scheme,” *BMC Genomics*, vol. 8, no. 1, pp. 1–12, 2007.

[36] M. E. Garber, O. G. Troyanskaya, K. Schluens et al., “Diversity of gene expression in adenocarcinoma of the lung,” *Proceedings of the National Academy of Sciences*, vol. 98, no. 24, pp. 13784–13789, 2001.

[37] M. T. Landi, T. Dracheva, M. Rotunno et al., “Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival,” *Plos One*, vol. 3, no. 2, article e1651, 2008.

[38] H. Okayama, T. Kohno, Y. Ishii et al., “Identification of genes upregulated in alk-positive and egrfr/kras/alk-negative lung adenocarcinomas,” *Cancer Research*, vol. 72, no. 1, pp. 100–111, 2012.

[39] S. Wachi, K. Yoneda, and R. J. B. Wu, “Interactome-transcriptome analysis reveals the high centrality of genes differentially expressed in lung cancer tissues,” *Bioinformatics*, vol. 21, no. 23, pp. 4205–4208, 2005.

[40] A. Bhattacharjee, W. G. Richards, J. Staunton et al., “Classification of human lung carcinomas by mrna expression profiling reveals distinct adenocarcinoma subclasses,” *Proceedings of the National Academy of Sciences*, vol. 98, no. 24, pp. 13790–13795, 2001.

[41] Y. Wang, H. Chen, J. Zhang, A. S. Cheng, J. Yu, and W. Kang, “Mcm family in gastrointestinal cancer and other malignancies: from functional characterization to clinical implication,” *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, vol. 1874, no. 2, article 188415, 2020.

[42] C. H. Y. Cheung, C. L. Hsu, K. P. Chen et al., “Mcm2-regulated functional networks in lung cancer by multi-dimensional proteomic approach,” *Scientific Reports*, vol. 7, no. 1, article 13302, 2017.

[43] Y. L. Fan, R. J. Liu, X. Y. Ding, X. Y. Shangguan, and X. R. Wu, “Deguelin Inhibits Proliferation and Regulates the Expression of mcm3-cdc45 in MCF-7 and h1299 Cells In Vitro,” in *Nan Fang yi ke da xue xue bao= Journal of Southern Medical University*, vol. 37, no. 11 pp. 1545–1550, University, 2017.

[44] I. Y. J. Genes, “Regulation of mcm2-7 function,” *Genes & Genetic Systems*, vol. 93, pp. 125–133, 2018.

[45] X. Sheng, H. Dai, Y. Du et al., “Lncrna carm overexpression promotes prognosis and chemosensitivity of triple negative breast cancer via acting as mir143-3p host gene and inhibiting DNA replication,” *Journal of Experimental & Clinical Cancer Research*, vol. 40, no. 1, pp. 1–17, 2021.

[46] D. He, B. Ren, S. Liu et al., “Oncogenic activity of amplified miniature chromosome maintenance 8 in human malignancies,” *Oncogene*, vol. 36, no. 25, pp. 3629–3639, 2017.

[47] E. M. Johnson, Y. Kinoshita, and D. C. Daniel, “A new member of the mcm protein family encoded by the human mcm8 gene, located contrapodal to gcd10 at chromosome band 20p12.3,” *Science Signaling*, vol. 6, no. 269, article pl1, 2013.

[48] D. He, B. Ren, S. Liu et al., “Oncogenic activity of amplified miniature chromosome maintenance 8 in human malignancies,” *Oncogene*, vol. 36, no. 25, pp. 3629–3639, 2017.

[49] M. Lutzmann, D. Maiorano, and M. J. G. Mechali, “Identification of full genes and proteins of mcm9, a novel, vertebrate-specific member of the mcm2-8 protein family,” *Gene*, vol. 362, pp. 51–56, 2005.

[50] M. Shao, S. Yang, and S. J. P. Dong, “High expression of mcm10 is predictive of poor outcomes in lung adenocarcinoma,” *PeerJ*, vol. 9, article e10560, 2021.

[51] K. Liu, M. Kang, X. Liao, and R. Wang, “Genome-wide investigation of the clinical significance and prospective molecular mechanism of minichromosome maintenance protein family genes in patients with lung adenocarcinoma,” *Plos One*, vol. 14, no. 7, article e0219467, 2019.

[52] S. G. Talbot, C. Estilo, E. Maghami et al., “Gene expression profiling allows distinction between primary and metastatic squamous cell carcinomas in the lung,” *Cancer Research*, vol. 65, no. 8, pp. 3063–3071, 2005.

[53] D. G. Beer, S. L. Kardia, C. C. Huang et al., “Gene expression profiles predict survival of patients with lung adenocarcinoma,” *Nature Medicine*, vol. 8, no. 8, pp. 816–824, 2002.