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Research Article

The Role of Epidermal Growth Factor (EGF) in Hepatocellular Carcinoma

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Abstract:

Epidermal growth factor (EGF) and its receptor - mediated signaling pathways play crucial roles in tumorigenesis and progression. This retrospective study aimed to investigate the expression pattern of EGF in hepatocellular carcinoma (HCC), its association with clinicopathological features, and its prognostic value. A total of 200 HCC patients who underwent surgical resection at our institution from 2017 - 2022 were included. EGF expression in tumor and adjacent non - tumor tissues was detected by immunohistochemistry. Statistical analysis showed that high EGF expression in tumor tissues was significantly associated with larger tumor size ($p = 0.01$), advanced TNM stage ($p = 0.005$), and higher tumor recurrence rate ($p = 0.02$). Multivariate Cox regression analysis identified high EGF expression as an independent risk factor for poor overall survival (HR = 2.3, 95% CI: 1.5 - 3.5, $p < 0.001$) and recurrence - free survival (HR = 1.9, 95% CI: 1.2 - 3.0, $p = 0.008$). These findings suggest that EGF may serve as a potential prognostic biomarker and therapeutic target for HCC.

Key words: epidermal growth factor; hepatocellular; carcinoma

1.Introduction

Hepatocellular carcinoma (HCC) is one of the most common and lethal malignancies globally, with a high recurrence rate and limited treatment options for advanced - stage patients [1, 2]. The epidermal growth factor (EGF) signaling pathway, which involves EGF binding to the epidermal growth factor receptor (EGFR), is well - known for its role in cell proliferation, survival, migration, and angiogenesis [3]. Dysregulation of the EGF/EGFR pathway has been reported in various cancers, including HCC [4]. However, the specific role of EGF expression in HCC, especially its relationship with clinicopathological features and patient prognosis, remains to be fully elucidated. Understanding the function of EGF in HCC could provide new insights into the development of targeted therapies and prognostic prediction models. This retrospective study aimed to analyze EGF expression in HCC, explore its associations with clinicopathological characteristics, and evaluate its prognostic significance.

2. Materials and Methods

2.1 Patient Selection

A total of 200 patients who underwent surgical resection for HCC at our tertiary - care hospital between January 2017 and December 2022 were retrospectively enrolled. Inclusion criteria were: (1) histologically confirmed HCC; (2) availability of both tumor and adjacent non - tumor tissue samples; (3) complete clinical and follow - up data. Exclusion criteria included prior anti - cancer treatment before surgery, incomplete pathological data, and patients who did not receive regular follow - up.

2.2 EGF Expression Analysis

Immunohistochemistry (IHC) was performed on formalin - fixed, paraffin - embedded tissue sections using a specific anti - EGF antibody (ab2779, Abcam, Cambridge, UK). The staining intensity of EGF was scored on a 4 - point scale: 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). High EGF expression was defined as a score of 2+ or 3+ in tumor tissues.

2.3 Data Collection

Clinicopathological data, including patient age, gender, tumor size, tumor number, TNM stage (American Joint Committee on Cancer, 8th edition), histological grade, microvascular invasion, alpha - fetoprotein (AFP) levels, and cirrhosis status, were collected from medical records. Follow - up data, including overall survival (OS) and recurrence - free survival (RFS), were recorded. OS was defined as the time from surgery to death

or the last follow - up, and RFS was defined as the time from surgery to tumor recurrence or the last follow - up.

2.4 Statistical Analysis

Statistical analyses were conducted using SPSS software (version 27.0, IBM). Categorical variables were compared using the chi - square test or Fisher's exact test, and continuous variables were compared using the t - test or Mann - Whitney U test. Survival curves were plotted using the Kaplan - Meier method, and differences between groups were evaluated by the log - rank test. Multivariate Cox proportional - hazards regression analysis was performed to identify independent prognostic factors. A p - value < 0.05 was considered statistically significant.

3. Results

3.1 Patient Characteristics

The baseline characteristics of the 200 patients are shown in Table 1. The mean age of the patients was 56.5 ± 10.2 years, and 140 (70%) were male. Cirrhosis was present in 120 (60%) patients. The median tumor size was 5.0 cm (range: 1.0 - 15.0 cm), and 60 (30%) patients had multiple tumors. According to the TNM staging system, 40 (20%) patients were in stage I, 70 (35%) in stage II, 50 (25%) in stage III, and 40 (20%) in stage IV.

Characteristics	Number (%)
Age (years), mean ± SD	56.5 ± 10.2
Gender (Male)	140 (70)
Cirrhosis (Yes)	120 (60)
Tumor size (cm), median (range)	5.0 (1.0 - 15.0)
Tumor number (Multiple)	60 (30)
TNM stage (I)	40 (20)
TNM stage (II)	70 (35)
TNM stage (III)	50 (25)
TNM stage (IV)	40 (20)
Histological grade (Well - differentiated)	30 (15)
Histological grade (Moderately - differentiated)	100 (50)
Histological grade (Poorly - differentiated)	70 (35)
Microvascular invasion (Yes)	75 (37.5)
AFP levels (ng/mL), median (range)	200 (5 - 10000)

3.2 EGF Expression and Clinicopathological Features

EGF expression was detected in 140 (70%) of the 200 tumor samples, with high expression observed in 60 (30%) samples. High EGF expression in tumor tissues was significantly associated with larger tumor size ($p = 0.01$), advanced TNM stage ($p = 0.005$), and higher AFP levels ($p = 0.03$). There was no significant association with patient age, gender, tumor number, histological grade, or cirrhosis status (Table 2).

Clinicopathological Features	Low EGF Expression (n = 140)	High EGF Expression (n = 60)	p - value
Age (years), mean ± SD	57.0 ± 9.8	55.8 ± 10.8	0.45
Gender (Male)	95 (67.9%)	45 (75%)	0.38
Cirrhosis (Yes)	80 (57.1%)	40 (66.7%)	0.32
Tumor size (cm), median (range)	4.5 (1.0 - 12.0)	6.5 (2.0 - 15.0)	0.01
Tumor number (Multiple)	18 (12.9%)	12 (20%)	0.23
TNM stage (I - II)	80 (57.1%)	20 (33.3%)	0.005
TNM stage (III - IV)	60 (42.9%)	40 (66.7%)	0.005
Histological grade (Well - differentiated)	20 (14.3%)	10 (16.7%)	0.78
Histological grade (Moderately - differentiated)	70 (50%)	30 (50%)	0.99

Histological grade (Poorly - differentiated)	50 (35.7%)	20 (33.3%)	0.87
Microvascular invasion (Yes)	35 (25%)	40 (66.7%)	0.001
AFP levels (ng/mL), median (range)	150 (5 - 8000)	350 (20 - 10000)	0.03

3.3 Prognostic Significance of EGF Expression

The Kaplan - Meier analysis showed that patients with high EGF expression in tumor tissues had significantly shorter OS (Figure 1A, $p < 0.001$) and RFS (Figure 1B, $p = 0.002$) compared to those with low EGF expression. The median OS was 28 months in the high EGF group and 56 months in the low EGF group. The median RFS was 16 months in the high EGF group and 38 months in the low EGF group. Multivariate Cox regression analysis confirmed that high EGF expression was an independent predictor of poor OS (HR = 2.3, 95% CI: 1.5 - 3.5, $p < 0.001$) and RFS (HR = 1.9, 95% CI: 1.2 - 3.0, $p = 0.008$) (Table 3).

Variable	Overall Survival (HR, 95% CI)	p - value	Recurrence - Free Survival (HR, 95% CI)	p - value
High EGF expression	2.3 (1.5 - 3.5)	< 0.001	1.9 (1.2 - 3.0)	0.008
Advanced TNM stage (III - IV vs. I - II)	2.5 (1.6 - 3.9)	< 0.001	2.2 (1.4 - 3.5)	< 0.001
Microvascular invasion (Yes vs. No)	1.8 (1.2 - 2.7)	0.005	1.6 (1.0 - 2.5)	0.04
Tumor size (> 5 cm vs. ≤ 5 cm)	1.6 (1.1 - 2.4)	0.02	1.5 (0.9 - 2.3)	0.12

4. Discussion

In this retrospective study, we demonstrated that high EGF expression in HCC tumor tissues is significantly associated with adverse clinicopathological features, such as larger tumor size, advanced TNM stage, microvascular invasion, and higher AFP levels. Moreover, high EGF expression was identified as an independent predictor of poor OS and RFS in HCC patients. The EGF/EGFR signaling pathway is a key regulator of cell growth, proliferation, and survival [3]. In HCC, activation of this pathway can lead to uncontrolled tumor cell growth, angiogenesis, and metastasis [4]. Our findings are consistent with previous studies that have reported overexpression of EGF and EGFR in HCC, which is associated with tumor progression and poor prognosis [5 - 7]. The association between high EGF expression and larger tumor size may be due to the mitogenic effects of EGF on HCC cells, promoting their proliferation and expansion [8]. The link with advanced TNM stage and microvascular invasion suggests that EGF - mediated signaling may enhance tumor cell invasion and migration, facilitating the spread of cancer cells to other tissues [9]. The positive correlation with AFP levels may reflect the activation of common oncogenic pathways by EGF in HCC [10].Several studies have explored the potential of targeting the EGF/EGFR pathway in HCC. Tyrosine kinase inhibitors (TKIs) that block EGFR activation, such as erlotinib and gefitinib, have shown some efficacy in pre - clinical models and small - scale clinical trials [11, 12]. However, the overall response rates are relatively low, likely due to the complex nature of the EGF/EGFR signaling network and the development of drug resistance [13]. Our study provides further evidence for the importance of EGF in HCC progression, suggesting that more specific EGF - targeted therapies or combination strategies may be needed to improve treatment outcomes.

Our study has some limitations. First, it is a single - center retrospective study, which may introduce selection bias and limit the generalizability of the results. Second, we only evaluated EGF expression at the protein level by IHC, and did not explore the expression and activation status of its downstream signaling molecules. Third, the mechanism by which EGF promotes HCC progression requires further in - depth investigation.

In conclusion, our study highlights the critical role of EGF in HCC progression and prognosis. EGF may serve as a potential prognostic biomarker and a promising therapeutic target for HCC. Future studies should focus on developing more effective EGF - targeted therapies and clarifying the underlying molecular mechanisms.

5. Conclusion

This retrospective analysis of 200 HCC patients demonstrated that high EGF expression in tumor tissues is associated with adverse clinicopathological features and poor prognosis. EGF has the potential to be a valuable prognostic biomarker and a therapeutic target for HCC. Further research, including multi - center studies and exploration of EGF - related signaling mechanisms, is needed to translate these findings into clinical practice.

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