Guanylate-binding protein 1 correlates with advanced tumor features, and serves as a prognostic biomarker for worse survival in lung adenocarcinoma patients

Quanchao Wan | Jingming Qu | Longfei Li | Feng Gao

Abstract
Objective: Guanylate-binding protein 1 (GBP1) is reported to promote tumor progression and treatment resistance in lung cancer, and presents as a prognostic biomarker in several solid tumors. However, the related research of GBP1 in clinical management of lung adenocarcinoma is still lacking. Therefore, the present study aimed to detect the clinical role of GBP1 in lung adenocarcinoma.

Methods: The clinical data of 221 lung adenocarcinoma patients were retrospectively analyzed, and then, their tumor tissue specimens and paired adjacent tissue specimens were retrieved for GBP1 detection via immunohistochemistry (IHC) assay.

Results: GBP1 expression was upregulated in tumor tissues compared with adjacent tissues ($P < .001$). Moreover, high tumor GBP1 expression was associated with larger tumor size ($P = .030$), positive lymph node (LYN) metastasis ($P = .001$), advanced TNM stage ($P = .001$), and abnormal preoperative carcinoembryonic antigen (CEA) level ($P = .026$). Furthermore, tumor GBP1 high expression was correlated with reduced disease-free survival (DFS) and overall survival (OS), and was of independent value in predicting worse DFS and OS. Additionally, data analysis of 1144 lung cancer patients derived from KMplot database (www.kmplot.com) further verified that GBP1 expression was negatively correlated with OS ($P = .009$).

Conclusion: GBP1 correlates with advanced tumor features and worse survival profiles, suggesting its value to be a prognostic biomarker in management of lung adenocarcinoma.

KEYWORDS
guanylate-binding protein 1, immunohistochemistry assay, lung adenocarcinoma, survival, tumor features

1 | INTRODUCTION

Lung cancer remains the leading contributor to cancer incidence, and represents approximately 20% cancer-related deaths globally.\(^1\)\(^2\) Lung adenocarcinoma is the most common subtype of lung cancer, and includes adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinomas.\(^3\) Despite the achievements in pathogenesis understanding and treatment...
advancements of lung adenocarcinoma, such as the development of individualized therapies, lung adenocarcinoma is still a devastating and aggressive tumor type considering the high risk of distant metastasis and acquired treatment resistance. Therefore, it is essential to explore the underlying mechanism of lung adenocarcinoma and look for novel prognostic biomarkers, assisting the management of lung adenocarcinoma.

Guanylate-binding protein 1 (GBP1) is a GTP-binding protein with a high GTPase activity, which interacts with various binding proteins involving in diverse biological functions, such as extracellular signaling, endosomal trafficking, and signal transduction. Furthermore, the role of GBP1 has been demonstrated in several lung-related diseases, which reveal that GBP1 is aberrantly expressed in patients with acute respiratory distress syndrome and pulmonary sarcoidosis. In addition, given that cancer emerges from a complex interaction among mutational events and cell state transitions accompanying by IFN-mediated inflammation, GBP1 is reported to participate in the oncogenic process of lung cancer. For example, GBP1 promotes tumor progression and paclitaxel resistance via activating Wnt/β-catenin signaling pathway in non–small-cell lung cancer (NSCLC). In addition, one study indicates that GBP1 promotes cell migration and invasion in lung adenocarcinoma. According to aforementioned evidence, we hypothesized that GBP1 might have potential to be a clinical prognostic biomarker of lung adenocarcinoma; however, there was no related study. Herein, we determined the expression of GBP1 in patients with lung adenocarcinoma, and further analyzed the correlation of GBP1 with clinical characteristics and prognosis of lung adenocarcinoma.

2 | MATERIALS AND METHODS

2.1 | Patients

This study retrospectively analyzed 221 patients with lung adenocarcinoma who underwent surgical resection in our hospital between January 2012 and December 2014. All analyzed patients met following criteria: (a) pathologically diagnosed as primary lung cancer; (b) histologically confirmed as lung adenocarcinoma; (c) age more than 18 years; (d) had well-preserved tumor and adjacent tissue specimens that were removed during the surgery; and (e) had complete preoperative clinical data and follow-up records that were able to use for assessment of disease-free survival (DFS) and OS. Patients who received neoadjuvant therapy before surgery, complicated with other cancers or without any follow-up data, were not included in the study. After surgery, patients received appropriate adjuvant therapy if clinically indicated (eg, chemotherapy and radiation therapy), according to NCCN guideline of NSCLC (NCCN: Non-Small Cell Lung Cancer Version 1.2013). The approval by Institutional Review Board of our hospital was obtained before initiation of study. The written informed consents were collected from patients or their family members.

2.2 | Data collection

Preoperative clinical data of patients were collected from the medical records, which covered age, gender, history of smoke, history of drink, hypertension, hyperlipidemia, diabetes, tumor differentiation, tumor size, lymph node (LYN) metastasis, TNM stage, and carcinoembryonic antigen (CEA) level. In addition, patients were followed up by clinic visits or telephone calls every 3-6 months. The survival data of patients were collected from follow-up records, which included disease status, disease relapse date, survival status, death date of patients, and last visit date. According to the survival data, DFS was calculated from the date of surgery to the date of disease relapse or patients’ death; OS was calculated from the date of surgery to the date of patients’ death or last visit. Patients who did not suffer from disease relapse or death were censored on the date of last visit in the survival analysis.

2.3 | Immunohistochemistry (IHC) assay

Totally 221 formaldehyde fixed, paraffin-embedded (FFPE) tumor tissue specimens and paired adjacent tissue specimens were collected from pathology department of our hospital. GBP1 expression in FFPE specimens was determined by IHC assay. Briefly, FFPE specimens were cut into 4-μm slices, mounted on positively charged glass slides and air-dried overnight. Next, the slices were deparaffinized in xylene and rehydrated in ethanol, then were quenched with fresh hydrogen peroxide to inhibit endogenous tissue peroxidase activity. After that, the slices were placed in antigen retrieval buffer and brought up to boil. Subsequently, slices were incubated with GBP1 polyclonal antibody (Thermo Fisher Scientific) at 4°C overnight. Next day, the slices were incubated with goat anti-rabbit IgG (H + L) secondary antibody (Thermo Fisher Scientific) at room temperature for 30 minutes. Afterward, slices were stained with diaminobenzidine and counterstained with hematoxylin. The slices were finally evaluated by investigator under a light microscopy.

2.4 | GBP1 expression evaluation

Based on the staining intensity and positively stained cell density, the GBP1 expression in the specimens was evaluated using a semi-quantitative scoring method as described in a previous study. The staining intensity was scored as 0, negative; 1, weak; 2, moderate; and 3, strong. The positively stained cell density was represented by percentage of positively stained cells, which was scored as: 0, 0%; 1, 1%-25%; 2, 26%-50%; 3, 51%-75%; and 4, 76%-100%. After...
multiplying the staining intensity score by the positively stained cell density score, a total IHC staining score of each specimen was obtained, which was ranging from 0 to 12. The total IHC staining score ≤3 was defined as GBP1 low expression; accordingly, total IHC staining score >3 was defined as GBP1 high expression.  

2.5 | Derived data of association between GBP1 and OS from KMplot database (www.kmplot.com)

We further verified the association between GBP1 and OS in 1144 lung cancer patients derived from an integrated database (KMplot, www.kmplot.com) of previously published transcriptomic datasets. The integrated database was developed as an online tool suitable for the real-time meta-analysis of published lung cancer microarray datasets to identify biomarkers related to survival, where univariate and multivariate Cox regression analysis, Kaplan-Meier survival plot with hazard ratio, and log-rank P value were calculated and plotted in R. The complete analysis tool could be accessed online at: www.kmplot.com/lung.

2.6 | Statistical analysis

All data analyses were carried out using SPSS 22.0 statistical software (IBM), and all graphs were plotted using GraphPad Prism 7.01 (GraphPad Software Inc). Clinical data were described as mean with standard deviation (SD), median with interquartile range (IQR), or number with percentage (No. (%)). GBP1 expression difference between tumor tissue and adjacent tissue was determined by McNemar’s test. Correlation of tumor GBP1 with clinical features of patients was determined by the chi-square test or the Spearman rank correlation test. Association between tumor GBP1 and DFS/OS was determined by log-rank test, which was displayed by the Kaplan-Meier curve. DFS-related factors and OS-related factors were identified by univariate and forward stepwise multivariate Cox’s proportional hazards regression analyses. Statistical significance level was defined as $P$ value <.05.

3 | RESULTS

3.1 | Clinical characteristics in patients with lung adenocarcinoma

The mean age of patients was 61.5 ± 10.8 years (Table 1). The number of male and female patients was 172 (77.8%) and 49 (22.2%), respectively. There were 32 (14.5%), 128 (57.9%), and 61 (27.6%) patients with well, moderate, and poor pathological differentiation, respectively. The average tumor size was 5.2 ± 2.1 cm. The number of patients with positive LYN metastasis was 79 (35.7%). As for TNM stage, the number of patients with TNM stages I, II, and III was 79 (35.7%), 59 (26.7%), and 83 (37.6%), respectively. The number of patients with abnormal preoperative CEA level (>5 ng/mL) was 132 (59.7%). The detailed information of clinical characteristics in patients with lung adenocarcinoma is shown in Table 1.

| Items                              | Patients (N = 221) |
|------------------------------------|-------------------|
| Age (y), mean ± SD                 | 61.5 ± 10.8       |
| ≤60 y, No. (%)                     | 109 (49.3)        |
| >60 y, No. (%)                     | 112 (50.7)        |
| Gender, No. (%)                    |                   |
| Male                               | 172 (77.8)        |
| Female                             | 49 (22.2)         |
| History of smoke, No. (%)          | 112 (50.7)        |
| History of drink, No. (%)          | 82 (37.1)         |
| Comorbidities, No. (%)             |                   |
| Hypertension                       | 80 (36.2)         |
| Hyperlipidemia                     | 64 (29.0)         |
| Diabetes                           | 30 (13.6)         |
| Pathological differentiation, No. (%) |                 |
| Well                               | 32 (14.5)         |
| Moderate                           | 128 (57.9)        |
| Poor                               | 61 (27.6)         |
| Tumor size (cm), mean ± SD         |                   |
| ≤5 cm                              | 136 (61.5)        |
| >5 cm                              | 85 (38.5)         |
| LYN metastasis, No. (%)            |                   |
| Negative                           | 142 (64.3)        |
| Positive                           | 79 (35.7)         |
| TNM stage, No. (%)                 |                   |
| Stage I                            | 79 (35.7)         |
| Stage II                           | 59 (26.7)         |
| Stage III                          | 83 (37.6)         |
| Preoperative CEA level (ng/mL), median (IQR) |       |
| Normal (≤5 ng/mL)                  | 89 (40.3)         |
| Abnormal (>5 ng/mL)                | 132 (59.7)        |

Abbreviations: CEA, carcinoembryonic antigen; IQR, interquartile range; LYN, lymph node; SD, standard deviation.

3.2 | Comparison of GBP1 expression between tumor and adjacent tissues in lung adenocarcinoma patients

After multiplying the staining intensity score by the positively stained cell density score, the total IHC staining score was ranging from 0 to 12. The total IHC staining score ≤3 was defined as GBP1 low expression, and total IHC staining score >3 was defined as GBP1 high expression. The representative example of GBP1 low and high expression in adjacent and tumor tissues is shown.
in Figure 1. Further comparative analysis indicated that, in tumor tissue, the proportion of GBP1 low expression and high expression were 51.6% and 48.4%, respectively; as for in adjacent tissue, the proportion of GBP1 low expression and high expression were 69.7% and 30.3%, respectively (Table 2). It is important that GBP1 expression was upregulated in tumor tissue compared with adjacent tissue (\(P < .001\)).

### 3.3 | Correlation of tumor GBP1 expression with clinical characteristics in lung adenocarcinoma patients

High tumor GBP1 expression was associated with larger tumor size (\(P = .030\)), positive LYN metastasis (\(P = .001\)), advanced TNM stage (\(P = .001\)), and abnormal preoperative CEA level (>5 ng/mL) (\(P = .026\)) (Table 3). However, there was no correlation of tumor GBP1 expression with age, gender, history of smoke, history of drink, hypertension, hyperlipidemia, diabetes, or pathological differentiation (all \(P > .05\)). The detailed information of clinical characteristics between tumor GBP1 high patients and tumor GBP1 low patients is displayed in Table 3.

### 3.4 | Correlation of tumor GBP1 expression with disease relapse and survival in lung adenocarcinoma patients

Further analysis compared the survival profiles between tumor GBP1 high patients and tumor GBP1 low patients, which observed that tumor GBP1 high expression was correlated with decreased DFS (\(P < .001\)) (Figure 2A) and OS (\(P < .001\)) (Figure 2B) in lung adenocarcinoma patients. Furthermore, the correlation of GBP1 with OS was further verified by the data of 1144 lung cancer patients derived from KMplot database (www.kmplot.com), which observed that OS was decreased in patients with GBP1 high expression compared to those with GBP1 low expression (\(P = .009\)) (Figure 3). However, this database was based on mRNA sequencing, which could not verify the correlation of GBP1 protein expression with OS.

### 3.5 | Factors affecting DFS in lung adenocarcinoma patients

To further detect the correlation of GBP1 expression with DFS in lung adenocarcinoma patients, we conducted univariate Cox’s proportional hazard regression and found that GBP1 high expression (HR = 1.828, \(P < .001\)), worse pathological differentiation (HR = 1.277, \(P = .033\)), tumor size >5 cm (HR = 1.458, \(P = .014\)), LYN metastasis positive (HR = 2.805, \(P < .001\)), higher TNM stage (HR = 1.477, \(P < .001\)), and preoperative CEA abnormal (>5 ng/mL) (HR = 1.526, \(P = .007\)) were correlated with worse DFS (Table 4). Further multivariate Cox’s proportional hazard regression revealed that GBP1 high expression (HR = 1.537, \(P = .004\)), LYN metastasis
TABLE 3 Correlation of tumor GBP1 expression with clinical features

| Items                        | Tumor GBP1 expression |          |          | P value |
|------------------------------|-----------------------|----------|----------|---------|
|                              | Low (n = 114)         | High (n = 107) |          |         |
| Age, No. (%)                 |                       |          |          |         |
| ≤60 y                        | 55 (48.2)             | 54 (50.5) | .741     |
| >60 y                        | 59 (51.8)             | 53 (49.5) |          |         |
| Gender, No. (%)              |                       |          |          |         |
| Male                         | 91 (79.8)             | 81 (75.7) | .461     |
| Female                       | 23 (20.2)             | 26 (24.3) |          |         |
| History of smoke, No. (%)    |                       |          |          |         |
| No                           | 52 (45.6)             | 57 (53.3) | .255     |
| Yes                          | 62 (54.4)             | 50 (46.7) |          |         |
| History of drink, No. (%)    |                       |          |          |         |
| No                           | 76 (66.7)             | 63 (58.9) | .231     |
| Yes                          | 38 (33.3)             | 44 (41.1) |          |         |
| Hypertension, No. (%)        |                       |          |          |         |
| No                           | 69 (60.5)             | 72 (67.3) | .296     |
| Yes                          | 45 (39.5)             | 35 (32.7) |          |         |
| Hyperlipidemia, No. (%)      |                       |          |          |         |
| No                           | 77 (67.5)             | 80 (74.8) | .237     |
| Yes                          | 37 (32.5)             | 27 (25.2) |          |         |
| Diabetes, No. (%)            |                       |          |          |         |
| No                           | 100 (87.7)            | 91 (85.0) | .562     |
| Yes                          | 14 (12.3)             | 16 (15.0) |          |         |
| Pathological differentiation, No. (%) |       |          |          |         |
| Well                         | 18 (15.8)             | 14 (13.1) | .698     |
| Moderate                     | 65 (57.0)             | 63 (58.9) |          |         |
| Poor                         | 31 (27.2)             | 30 (28.0) |          |         |
| Tumor size, No. (%)          |                       |          |          |         |
| ≤5 cm                        | 78 (68.4)             | 58 (54.2) | .030     |
| >5 cm                        | 36 (31.6)             | 49 (45.8) |          |         |
| LYN metastasis, No. (%)      |                       |          |          |         |
| Negative                     | 85 (74.6)             | 57 (53.3) | .001     |
| Positive                     | 29 (25.4)             | 50 (46.7) |          |         |
| TNM stage, No. (%)           |                       |          |          |         |
| Stage I                      | 52 (45.6)             | 27 (25.2) | .001     |
| Stage II                     | 29 (25.4)             | 30 (28.0) |          |         |
| Stage III                    | 33 (28.9)             | 50 (46.8) |          |         |
| Preoperative CEA level, No. (%) |                  |          |          |         |
| Normal (>5 ng/mL)            | 54 (47.4)             | 35 (32.7) | .026     |
| Abnormal (<5 ng/mL)          | 60 (52.6)             | 72 (67.3) |          |         |

Abbreviations: CEA, carcinoembryonic antigen; GBP1, Guanylate-binding protein 1; LYN, lymph node.

positive (HR = 2.495, P < .001), and preoperative CEA abnormal (>5 ng/mL) (HR = 1.409, P = .029) were independent factors for reduced DFS.

3.6 | Factors affecting OS in lung adenocarcinoma patients

To further detect the correlation of GBP1 expression with OS in lung adenocarcinoma patients, univariate Cox's proportional hazard regression was performed, which observed that GBP1 high expression (HR = 2.218, P < .001), worse pathological differentiation (HR = 1.367, P = .013), tumor size >5 cm (HR = 1.620, P = .004), LYN metastasis positive (HR = 3.506, P < .001), higher TNM stage (HR = 1.430, P < .001), and preoperative CEA abnormal (>5 ng/mL) (HR = 2.058, P < .001) were correlated with decreased OS (Table 5). Further multivariate Cox's proportional hazard regression revealed that GBP1 high expression (HR = 1.756, P = .001), worse pathological differentiation (HR = 1.301, P = .044), LYN metastasis positive (HR = 3.023, P < .001), and preoperative CEA abnormal (>5 ng/mL) (HR = 1.917, P < .001) were independent factors for decreased OS.

4 | DISCUSSION

GBP1 is an important member of the GTPase family, and its structure consists of two domains, including a N-terminal globular domain with GTPase activity and a C-terminal α-helical domain.16 Several recent studies reveal the involvement of GBP1 in the underlying mechanism of different tumors, such as prostate cancer, ESCC, and ovarian cancer.11,17,18 For example, mechanically, GBP1 promotes cell proliferation, migration, and invasion, and increases the level of mitochondrial oxidative phosphorylation and glycolysis in prostate cancer cells, enhancing progression and aggression of prostate tumor.11 Further clinical correlation analysis exhibits that GBP1 is correlated with aggressive clinical features and shorter survival profiles in prostate cancer patients.11 In addition, the implication of GBP1 in lung cancer is indicated by previous publication, which reports that GBP1 enhances cell motility to promote lung adenocarcinoma invasiveness.12 However, the correlation of GBP1 with clinical characteristics and prognosis is not determined in lung adenocarcinoma patients yet, which was explored in our present study.

In our present study, we detected GBP1 expression in tumor and pair adjacent tissues of lung adenocarcinoma patients via IHC assay and found that GBP1 was upregulated in lung adenocarcinoma tissues compared with paired adjacent tissues. The possible reasons might include that (a) according to previous studies, GBP1 might have pro-survival effects on some oncogenic mutations, such as EGFR mutation, leading to EGFR mutation-driven tumorigenicity of lung adenocarcinoma19; and (b) in addition, GBP1 might exert oncogenic effect and its high expression might activate oncogenic Wnt/β-catenin signaling pathway, contributing to the initiation of lung adenocarcinoma.10

Furthermore, we further detected the correlation of GBP1 with clinical characteristics in lung adenocarcinoma patients, and found that its high expression was correlated with larger tumor size, presence of LYN metastasis, advanced TNM stage, and abnormal preoperative CEA level, suggesting the positive correlation of GBP1...
with advanced tumor features of lung adenocarcinoma. The possible reasons might include that (a) based on the correlation of GBP1 with EGFR mutation, GBP1 might lead to autophosphorylation of receptor tyrosine kinase via activating EGFR, initiating a cascade of downstream signaling pathway, and further resulting in cellular proliferation, differentiation, and survival of lung adenocarcinoma. Therefore, high GBP1 expression was correlated with development and progression of lung adenocarcinoma20, and (b) in addition, GBP1 was reported to be involved in the actin cytoskeleton remodeling process that was an essential event in cell migration, and therefore, we speculated that GBP1 high expression might promote cell motility and invasiveness of lung adenocarcinoma, and further correlate with LYN metastasis and advanced TNM stage in lung adenocarcinoma patients.21

Previous evidence has indicated the correlation of GBP1 with the development of treatment resistance.10,11,22 For example, GBP1 is correlated with ovarian tumor recurrence after paclitaxel or docetaxel therapies, and its high expression predicts a significantly decreased progression-free survival in ovarian cancer patients.10 As for in NSCLC, another experimental study reveals that drug resistance to paclitaxel is reversed after the GBP1 knockdown in NSCLC cells with paclitaxel resistance.22 In addition, considering the correlation of GBP1 with advanced tumor features in lung adenocarcinoma patients and given the correlation of GBP1 with therapy resistance in tumor treatment, further analysis was conducted to explore the association of GBP1 with survival profiles in the patients recruited in the present study.10,11,22 The results observed that GBP1 was negatively correlated with reduced DFS and OS, and was of independent value in predicting worse DFS and OS in lung adenocarcinoma patients. This result was further validated by the data derived from KMplot database, and these results both suggested that GBP1 presented value to be a prognostic biomarker in lung adenocarcinoma. The possible reasons might involve that (a) firstly, according to prior results, GBP1 high expression was associated with advanced tumor features in lung adenocarcinoma patients, which were considered to be high risk factors for poor prognosis. Therefore, lung adenocarcinoma patients with higher GBP1 expression presented with poor survival23; (b) secondly, GBP1 might promote the invasiveness of lung adenocarcinoma via promoting cell motility, increasing the recurrence risk and contributing to undesirable survival profiles in patients with lung adenocarcinoma12; (c) thirdly, considering the correlation of GBP1 with increased chemotherapy resistance, patients with GBP1 high expression might
TABLE 4 DFS-related factors

| Items                                      | Cox’s proportional hazard regression | P value |
|--------------------------------------------|--------------------------------------|---------|
| Univariate Cox’s regression                |                                      |         |
| GBP1 high expression                       | 1.829 (1.357-2.465)                  | <.001   |
| Age > 60 y                                 | 1.178 (0.876-1.586)                  | .278    |
| Male                                       | 1.109 (0.769-1.600)                  | .578    |
| History of smoke                           | 0.940 (0.700-1.262)                  | .680    |
| History of drink                           | 1.214 (0.897-1.642)                  | .209    |
| Hypertension                               | 1.051 (0.772-1.432)                  | .751    |
| Hyperlipidemia                             | 1.111 (0.801-1.539)                  | .529    |
| Diabetes                                   | 1.305 (0.860-1.980)                  | .211    |
| Worse pathological differentiation          | 1.277 (1.020-1.598)                  | .033    |
| Tumor size > 5 cm                          | 1.458 (1.079-1.970)                  | .014    |
| LYN metastasis positive                    | 2.805 (2.063-3.816)                  | <.001   |
| Higher TNM stage                           | 1.477 (1.237-1.763)                  | <.001   |
| Preoperative CEA abnormal (> 5 ng/mL)      | 1.526 (1.125-2.070)                  | .007    |

Multivariate Cox’s regression (forward stepwise)

| Items                                      | Cox’s proportional hazard regression | P value |
|--------------------------------------------|--------------------------------------|---------|
| GBP1 high expression                       | 1.573 (1.159-2.134)                  | .004    |
| LYN metastasis positive                    | 2.495 (1.822-3.415)                  | <.001   |
| Preoperative CEA abnormal (> 5 ng/mL)      | 1.409 (1.036-1.915)                  | .029    |

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; GBP1, Guanylate-binding protein 1; HR, hazard ratio; LYN, lymph node.

present reduced treatment response, and further long-term worse survival profiles.11,22 Furthermore, as the current study was a single-center study with a relatively small sample size, there therefore might exist sampling bias and limited generalization, which contributed to more significant in the study samples compared with that extracted from KMplot database.

There still existed some limitations in present study as follows: (a) Firstly, the present study was a single-center study with a relatively small sample size; therefore, further studies recruiting more patients from multiple centers were needed for validation. (b) Secondly, the detailed mechanism of GBP1 involving in molecular pathways driving tumor progression and its contribution to treatment resistance in lung adenocarcinoma needed further cellular experiments for investigation. (c) Thirdly, our study only detected the protein expression of GBP1 by IHC assay, and more detection techniques (such as reverse transcription quantitative polymerase chain reaction used for GBP1 mRNA quantification) were needed to further validating the results. (d) Fourthly, the present study only included the patients with lung adenocarcinoma; therefore, the value of GBP1 as a prognostic biomarker in the management of lung squamous cell carcinoma needed further exploration. (e) Fifthly, the median of follow-up duration was 56 months (range: 2 months-96 months), and longer follow-up period was needed for further validating the long-term clinical role of GBP1 in the management of lung adenocarcinoma.

In conclusion, GBP1 is correlated with advanced tumor features, unfavorable DFS, and OS, suggesting its potential as a prognostic biomarker in management of lung adenocarcinoma.

ORCID
Feng Gao https://orcid.org/0000-0001-5888-6412

REFERENCES
1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Chun YJ, Choi JW, Hong MH, et al. Molecular characterization of lung adenocarcinoma from Korean patients using next generation sequencing. PloS One. 2019;14(11):e0224379.
3. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(4):504-535.
4. Zhang XU, Maity T, Kashyap MK, et al. Quantitative tyrosine phosphoproteomics of epidermal growth factor receptor (EGFR)
tyrosine kinase inhibitor-treated lung adenocarcinoma cells reveals potential novel biomarkers of therapeutic response. Mol Cell Proteomics. 2017;16(5):891-910.

5. Honkala AT, Tailor D, Malhotra SV. Guanylate-binding protein 1: an emerging target in inflammation and cancer. Front Immunol. 2019;10:3139.

6. Unterer B, Wiesmann V, Gunasekaran M, et al. IFN-gamma-response mediator GBP-1 represses human cell proliferation by inhibiting the Hippo signaling transcription factor TEAD. Biochem J. 2018;475(18):2955-2967.

7. Saunders NA, Smith RJ, Jetten AM. Differential responsiveness of human bronchial epithelial cells, lung carcinoma cells, and bronchial fibroblasts to interferon-gamma in vitro. Am J Respir Cell Mol Biol. 1994;11(2):147-152.

8. Li H, Zhao X, Wang J, et al. Bioinformatics analysis of gene expression profile data to screen key genes involved in pulmonary sarcoidosis. Gene. 2017;596:98-104.

9. Kong SL, Chui P, Lim B, et al. Elucidating the molecular physiopathology of acute respiratory distress syndrome in severe acute respiratory syndrome patients. Virus Res. 2009;145(2):260-269.

10. Song J, Wei QY. GBP1 promotes non-small cell lung carcinoma malignancy and chemoresistance via activating the Wnt/beta-catenin signaling pathway. Eur Rev Med Pharmacol Sci. 2020;24(10):5465-5472.

11. Cheng L, Gou L, Wei T, et al. GBP1 promotes erlotinib resistance via PKG1-activated EMT signaling in non-small cell lung cancer. Int J Oncol. 2020;57(3):858-870.

12. Yamakita I, Mimae T, Tsutani Y, et al. Guanylate binding protein 1 (GBP-1) promotes cell motility and invasiveness of lung adenocarcinoma. Biochem Biophys Res Commun. 2019;518(2):266-272.

13. Ettinger DS, Akerley W, Borghaei H, et al. Non-small cell lung cancer, version 2.2013. J Natl Compr Canc Netw. 2013;11(6):645–653; quiz 653.

14. Tian Y, Zhao KE, Yuan L, et al. EIF3B correlates with advanced disease stages and poor prognosis, and it promotes proliferation and inhibits apoptosis in non-small cell lung cancer. Cancer Biomark. 2018;23(2):291-300.

15. Gyorffy B, Surowiak P, Budczies J, et al. Online survival analysis software to assess the prognostic value of biomarkers using transcriptomic data in non-small cell lung cancer. PLoS One. 2013;8(12):e82241.

16. Prakash B, Renault L, Praefcke GJ, et al. Triphosphate structure of guanylate-binding protein 1 and implications for nucleotide binding and GTPase mechanism. EMBO J. 2000;19(17):4555-4564.

17. Li L, Ma G, Jing C, et al. Guanylate-binding protein 1 (GBP1) promotes lymph node metastasis in human esophageal squamous cell carcinoma. Discov Med. 2015;20(112):369-378.

18. Zhao J, Li X, Liu L, et al. Oncogenic role of guanylate binding protein 1 in human prostate cancer. Front Oncol. 2019;9:1494.

19. Lan Q, Wang A, Cheng Y, et al. Guanylate binding protein-1 mediates EGFRvIII and promotes glioblastoma growth in vivo but not in vitro. Oncotarget. 2016;7(9):9680-9691.

20. Singh D, Kumar Attri B, Kaur Gill R, et al. Review on EGFR inhibitors: critical updates. Mini Rev Med Chem. 2016;16(14):1134-1166.

21. Ostler N, Britzen-Laurent N, Liebl A, et al. Gamma interferon-induced guanylate binding protein 1 is a novel actin cytoskeleton remodelling factor. Mol Cell Biol. 2014;34(2):196-209.

22. Wadi S, Tipton AR, Trendel JA, et al. HGBP-1 expression predicts shorter progression-free survival in ovarian cancers, while contributing to paclitaxel resistance. J Cancer Ther. 2016;7(13):994-1007.

23. Zhu W-Y, Li H-F, Fang K-X, et al. Epidermal growth factor receptor mutations and their prognostic value with carcinoembryonic antigen in pathological T1 lung adenocarcinoma. Dis Markers. 2018;2018:2942618.

How to cite this article: Wan Q, Qu J, Li L, Gao F. Guanylate-binding protein 1 correlates with advanced tumor features, and serves as a prognostic biomarker for worse survival in lung adenocarcinoma patients. J Clin Lab Anal 2021;35:e23610. https://doi.org/10.1002/jcla.23610