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ORIGINAL RESEARCH

Pyroptosis-Mediator GSDMD in Plasma: A Potent Biomarker Lung Cancer Diagnosis and Prognosis Assessment

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Objective: Lung cancer's high mortality is linked to late diagnosis, with current methods having limitations. This study aimed to evaluate the diagnostic efficacy of Gasdermin D (GSDMD) in lung cancer and explore its biological functions.

Methods: A total of 114 lung cancer patients, 87 patients with pulmonary nodules, and 100 healthy controls were enrolled. Clinical data were collected, and venous blood samples were obtained. GSDMD, carcinoembryonic antigen (CEA), neuron - specific enolase (NSE), cytokeratin 19 fragment (CYFRA21 - 1), and other markers were measured using specific assays. Statistical analysis, including variance tests, ANOVA, and logistic regression, was performed to analyze the data.

Results: There were no significant differences in age and gender among the three groups. However, GSDMD levels were highest in the lung cancer group, followed by the pulmonary nodule group, and lowest in the healthy control group ($P < 0.05$). GSDMD was positively correlated with multiple biomarkers such as CEA ($r = 0.329$, $P < 0.001$), NSE ($r = 0.266$, $P < 0.001$), and CYFRA21 - 1 ($r = 0.477$, $P < 0.001$). Multivariate logistic regression analysis indicated that serum GSDMD, CEA, SCC, HE4, and IL - 6 were independent risk factors for lung cancer. The area under the ROC curve (AUC) of plasma GSDMD was 0.860, higher than that of CEA (0.801) and SCC (0.843). At a plasma GSDMD cut - off value of 39.87 pg/mL, the diagnostic sensitivity was 95.6%, and the specificity was 72.2%. When combined with other biomarkers (CEA, SCC, and HE4), the AUC reached 0.959, with a sensitivity of 93.0% and a specificity of 82.9%.

Conclusion: GSDMD holds promise as a diagnostic/prognostic biomarker for lung cancer, alone or combined with other markers, enhancing risk assessment accuracy to aid early detection and improve outcomes.

Keywords: lung cancer, gasdermin D, biomarker, diagnosis, prognosis, inflammation, tumor markers

Introduction

Lung cancer remains one of the most lethal malignancies worldwide, with a disproportionate impact on both developed and developing nations. According to GLOBOCAN 2020 data, lung cancer constitutes 11.4% of all new cancer cases and 18.0% of cancer-related deaths globally, surpassing breast and colorectal cancers in mortality burden. Lung cancer continues to be a major global health challenge, with its pathogenesis driven by a dynamic interplay of modifiable and non-modifiable risk factors. Cigarette smoking remains the predominant contributor, responsible for nearly 80–90% of cases, as highlighted by recent meta-analyses confirming the dose-dependent relationship between smoking duration and adenocarcinoma risk. Lung cancer stands as the most frequently diagnosed type of cancer and is also the primary cause of cancer-related mortality among males. Non-small cell lung cancer (NSCLC) constitutes roughly 80% of all lung cancer cases.[1] Regrettably, the vast majority of patients afflicted with NSCLC are diagnosed with the carcinoma at a stage where they already have locally advanced or metastatic disease[2,3]. Despite advances in therapeutic strategies, the 5-year survival rate for lung cancer patients remains dismal, largely due to late-stage diagnosis exacerbated by socioeconomic disparities

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in screening access.[4] Current diagnostic approaches primarily rely on imaging modalities and tumor biomarker assays, yet both exhibit significant limitations that hinder early detection and accurate diagnosis.

Computed tomography (CT) and other imaging technologies form the basis of lung cancer screening. However, high-resolution CT has not yet achieved optimal specificity in detecting small lung nodules, leading to frequent false positives and unnecessary invasive surgeries.[5,6] Additionally, research indicates that radiomics is poised to become an advanced AI-driven imaging characterization technique capable of directly predicting the response to immunotherapy for various solid tumors, a method that has been extensively studied in NSCLC.[7,8] Tumor biomarker assays, including carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA 21–1), and neuron-specific enolase (NSE), are non-invasive alternatives. However, their clinical utility is hampered by low sensitivity (40–60%) and specificity (75–85%) in early-stage disease, as well as cross-reactivity with benign conditions For instance, CYFRA 21–1 exhibits poor performance in squamous cell carcinoma detection, while NSE is unreliable for small-cell lung cancer due to interference from hemolysis. Such constraints highlight the urgent demand for novel biomarkers with higher diagnostic accuracy.

The discovery of new biomarkers is critical to revolutionizing lung cancer diagnostics. Glycodelin-derived spliceosome-mediated RNA debris (GDSMD), a recently identified splice variant of the glycodelin family, has emerged as a promising candidate. Gasdermin D (GSDMD), a key executioner of pyroptosis, has emerged as a pivotal molecule in cancer biology. As a substrate for inflammatory caspases (caspase-1/4/5/11), GSDMD is cleaved into N-terminal (GSDMD-N) and C-terminal (GSDMD-C) fragments. The N-terminal oligomerizes to form plasma membrane pores, facilitating the release of pro-inflammatory cytokines (eg, IL-1β, IL-18) and promoting immunogenic cell death, while the C-terminal fragment suppresses apoptosis.[9,10] In lung cancer, aberrant GSDMD expression correlates with tumor microenvironment remodeling and chemotherapy resistance, yet its dual role—either activating anti-tumor immunity or driving pro-tumorigenic inflammation—remains poorly understood.[11] The canonical pathway of gasdermin D (GSDMD)-induced pyroptosis is primarily initiated by NLRP1 inflammasomes. Exogenous pathogens and endogenous damage signals are recognized by other inflammasome sensors, including NLRC4, NLRP3, and AIM2. The activation of these inflammasomes underscores the critical link between pyroptosis and the tumor immune microenvironment. Studies have demonstrated that NLRP1 inflammasomes can be activated by dipeptidyl peptidase (DPP). Once activated, NLRP1 promotes the secretion of pro-inflammatory cytokines and enhances Th1 cell-mediated immune responses. This process not only amplifies the therapeutic efficacy of anti-PD1 antibodies in tumor treatment but also reduces the infiltration of CD8+ T cells at metastatic sites, suggesting a dual role in modulating anti-tumor immunity.[12] Despite its potential, the diagnostic relevance of GDSMD in human lung cancer remains unexplored, and its mechanistic role in disease progression is poorly understood.

Studies have shown the biological function of GSDMD in non-small cell lung cancer (NSCLC). GSDMD protein levels are significantly upregulated in NSCLC. High GSDMD expression is associated with aggressive features, including larger tumors and more advanced lymph node metastasis (TNM) staging. High GSDMD expression in lung adenocarcinoma (LUAD) indicates poor prognosis, and GSDMD knockout inhibits tumor growth in vitro and in vivo. In GSDMD-deficient tumor cells, both endogenous and exogenous activation of the pyroptotic (NLRP3/caspase-1) signaling pathway induces another type of programmed cell death (apoptosis). GSDMD depletion activates caspase-3 and PARP cleavage and promotes cancer cell death through the intrinsic mitochondrial apoptosis pathway.

This research focuses on assessing the effectiveness of GSDMD in the diagnosis of lung cancer and delving deeply into its biological functions. We are committed to bridging the critical gaps in non - invasive diagnosis. Meanwhile, we aim to conduct an in - depth exploration of the predictive value of the combined diagnosis of GSDMD with other markers. If GSDMD can be successfully validated, it will lay the foundation for its integration into the clinical workflow. Ultimately, this will lead to an increase in the early detection rate of lung cancer and an improvement in patient prognosis.

Materials and Methods

Study Population

In the lung cancer group, 114 lung cancer patients who visited the Thoracic Surgery Department of Hebei General Hospital from January 2024 to November 2024 were collected. There were 63 males and 51 females, with an average age of (61.14 ± 8.30) years. The benign group consisted of 87 patients with pulmonary nodules hospitalized during the same

period, including 40 males and 47 females, with an average age of (59.31 ± 11.64) years. Retrospective analysis was carried out with 100 healthy subjects in the same period as the control group, who were matched with the lung cancer and pulmonary nodule patients in terms of gender and age.

Inclusion and Exclusion Criteria

Inclusion criteria: Patients hospitalized for the first time for lung cancer treatment; untreated lung cancer patients; lung cancer patients diagnosed by surgery, lung biopsy, or fiberoptic bronchoscopy biopsy; lung cancer patients with good compliance and complete case records. Exclusion criteria: Patients with incomplete medical records and basic information; patients with other tumors or systemic diseases.This study was approved by the Ethics Committee of Hebei General Hospital [Approval Number: 2024(288)]. Informed consent was obtained from all participants.

Collection of Clinical Data

Data were collected on patient gender, age, GSDMD, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), cytokeratin 19 fragment (CYFRA21-1), squamous epithelial cell carcinoma antigen (SCC), gastrin-releasing peptide precursor (ProGRP), human ependynein 4 (HE4), interleukin 6 (IL-6), and C-reactive protein (CRP) were collected.

Sample Collection

All subjects were required to fast for at least 12 hours. The next morning, 5 mL of non-anticoagulated venous blood was collected on an empty stomach and allowed to clot at room temperature for 2 hours. After centrifugation (1000×g, 4°C, 15 min), the serum was collected and stored in a refrigerator at −80°C until use.

The plasma concentration of Gasdermin D (GSDMD) was quantified through a chemiluminescence assay provided by Beijing Meide Taikang Biotechnology Co., Ltd. The operations were strictly in accordance with the instructions of the reagent kits.

The intra-assay and inter-assay variability of GSDMD measurements were <8% and <15%, respectively.CRP was measured by immunoturbidimetric assay using a Beckman AU5800 automated biochemical analyzer and its associated reagents.

Tumor markers and IL-6 were measured by Roche 602 electrochemiluminescence analyzer, and the measurements were strictly carried out according to the reagent instructions and the operation procedures of the instrument.

Statistical Analysis

Data analysis and graphing were performed using SPSS 25.0 software and GraphPad Prism 8.0. Measurement data that follow a normal distribution are presented as the mean±standard deviation (X±S), whereas non - normally distributed data are expressed as the median (Q1,Q3). Given the emphasis of this study on multiple comparisons, a variance homogeneity test was carried out.For data exhibiting homogeneous variances, one - way ANOVA was applied, and this was succeeded by multiple comparisons using the Least Significant Difference (LSD) method. When variances were non - homogeneous, non - parametric tests were utilized. Specifically, the Kruskal–Wallis test was employed for multiple - group comparisons, and the Bonferroni correction was used for pairwise comparisons.Qualitative data were analyzed via chi - square tests. Additionally, Spearman's rank correlation analysis was conducted to evaluate the relationship between plasma GSDMD levels and clinical indicators.Additionally, multiple logistic regression analysis was conducted to identify risk factors for the onset of lung cancer (LC). The cutoff value was determined using the Youden index.The diagnostic value of plasma GSDMD for LC was evaluated using the area under the receiver operating characteristic curve (AUC). We performed collinearity diagnostics on the study variables and found no evidence of multicollinearity. See Supplementary Material. All statistical tests employed a two - tailed approach, with the significance level set at a stringent $P < 0.05$.

Results

Comparison of Clinical Indicators Among Newly Diagnosed Lung Cancer, Pulmonary Nodule, and Healthy Controls

There were no statistically significant differences in age and gender among the three groups of patients. Nevertheless, substantial disparities emerged in other measurements across the three groups, with a statistically significant difference ($P < 0.05$, Tables 1).

Table 1 Comparison of Clinical Indicators Between Lung Cancer, Lung Nodules, and Healthy Control Groups

Projects	Lung Cancer Group (LC)	Pulmonary Nodule Group (PN)	Healthy Control Group (HC)	$X^2/F/H$	*P Value*
Gender (male/female)	63/51	40/47	56/44	2.314	0.314
Age(year)	61.14±8.30	59.31±11.64	58.37±8.82	2.867	0.059
GSDMD (pg/mL)	94.05 (65.21~124.21)*,#	51.67 (30.25~96.69)Δ	5.06 (2.98~7.17)	206.781	0.000
CYFRA21-1 (ng/mL)	3.27 (2.19~6.33)*,#	2.20 (1.57~3.13)Δ	1.47 (1.19~1.94)	98.292	0.000
SCC (ng/mL)	1.69 (1.32~2.35)*,#	1.30 (0.98~1.74)Δ	0.46 (0.35~0.63)	192.234	0.000
CRP (mg/L)	8.04 (1.69~39.27)*,#	2.01 (1.13~3.01)Δ	0.46 (0.14~1.40)	99.632	0.000
NSE (ng/mL)	14.55 (9.87~18.35) #	12.63 (10.57~15.47)Δ	11.61 (9.88~12.77)	27.279	0.000
ProGRP (pg/mL)	41.09 (30.03~65.69) #	39.30 (32.86~50.17)Δ	27.35 (23.32~30.85)	96.139	0.000
CEA (ng/mL)	4.15 (2.15~11.12)*,#	1.78 (1.08~2.54)	1.46 (0.93~2.23)	77.6	0.000
HE4 (pmol/L)	93.92 (66.45~172.43)*,#	51.17 (41.80~62.06)	45.77 (39.32~51.65)	141.586	0.000
IL-6 (pg/mL)	102.10 (30.99~218.40)*,#	2.50 (1.50~3.81)	2.34 (1.71~3.65)	169.286	0.000

Note: *Indicated comparison between the lung cancer group and the pulmonary nodule group had a statistically difference; # indicated comparison between the lung cancer group and the healthy control group had a statistically difference; Δ indicated comparison between the pulmonary nodule group and the healthy control group had a statistically difference.

In the lung cancer group, the levels of GSDMD, CYFRA21 - 1, SCC, and CRP were the highest, followed by those in the lung nodule group, and were the lowest in the healthy control group ($P < 0.05$; see (Figure 1a–d). The levels of NSE and ProGRP were significantly higher in both the lung cancer group and the lung nodule group than in the healthy control group ($P < 0.05$). Nevertheless, there was no significant difference between the lung cancer group and the lung nodule group (Figure 1e and f). The levels of CEA, HE4, and IL - 6 were significantly higher in the lung cancer group compared to the lung nodule group ($P < 0.05$). However, no significant differences were observed between the lung nodule group and the healthy control group (Figure 1g–i).

Correlation Analysis Between Plasma GSDMD and Markers of Inflammation and Tumor Markers

Spearman's analysis indicated correlations between GSDMD and various markers: GSDMD and CEA ($r = 0.329$, $P < 0.001$, Figure 2A), GSDMD and NSE ($r = 0.266$, $P < 0.001$, Figure 2B), GSDMD and CYFRA21 - 1 ($r = 0.477$, $P < 0.001$,Figure 2C), GSDMD and SCC ($r = 0.648$, $P < 0.001$, Figure 2D), GSDMD and ProGRP ($r = 0.379$, $P < 0.001$, Figure 2E), GSDMD and HE4 ($r = 0.468$, $P < 0.001$, Figure 2F), GSDMD and IL - 6 ($r = 0.616$, $P < 0.001$, Figure 2G), as well as GSDMD and CRP ($r = 0.226$, $P < 0.001$, Figure 2H) (Table 2).

An Analytical Exploration of the Factors Affecting the Progression of Newly - Diagnosed Lung Cancer

Binary logistic regression analysis was carried out, taking the occurrence or non - occurrence of lung cancer as the dependent variable, while GSDMD, CEA, NSE, CYFRA21 - 1, SCC, ProGRP, HE4, IL - 6, and CRP were regarded as independent variables.The findings from univariate logistic regression revealed that all the observed indicators were independent influencing factors. The results of multivariate logistic regression showed that serum GSDMD, CEA, SCC, HE4, and IL - 6 were independent risk factors for lung cancer ($P < 0.05$) (Table 3).

The Predictive Significance of Plasma - Based GSDMD in the Realm of Lung Cancer

The area under the ROC curve (AUC) of plasma GSDMD, registering at 0.860, outstripped those of CEA (0.801) and SCC (0.843). Even though it fell short of HE4's AUC (0.901), the sensitivity of GSDMD soared to 95.6%, substantially higher than HE4's 83.3%. This indicates that plasma GSDMD also boasts a relatively high diagnostic value among the individual biomarkers for lung cancer.

At a plasma GSDMD cut - off value of 39.87 pg/mL, the diagnostic sensitivity hit 95.6%, and the specificity stood at 72.2% (Table 4 and Figure 3).

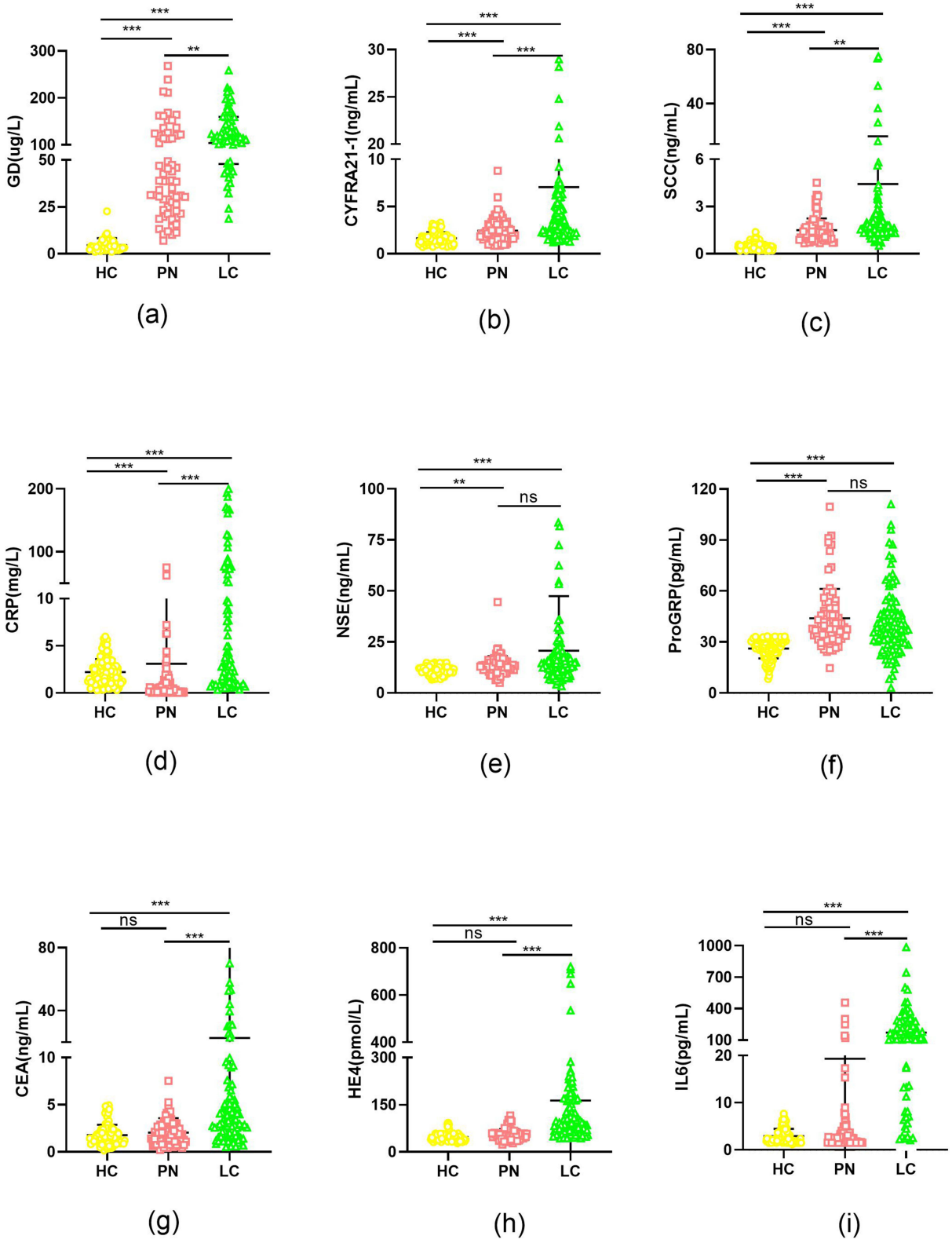

Figure 1 Plasm levels of GD(**a**), CEA(**b**), NSE(**c**), CYFRA21-1(**d**), SCC(**e**), ProGRP (**f**), HE4(**g**), IL6(**h**) and CRP(**i**) in Healthy Control group, Pulmonary Nodule group and Lung Cancer group.

Note: **p < 0.01, ***p<0.001, ns: There was no statistical difference between the two groups.

Abbreviations: GD, Gasdermin D;CEA, carcinoembryonic antigen;NSE, neuron-specific enolase; CYFRA21-1, cytokeratin 19 fragment; SCC, squamous epithelial cell carcinoma antigen; ProGRP, gastrin-releasing peptide precursor; HE4, human ependynein 4; IL-6, interleukin 6; CRP, C-reactive protein.

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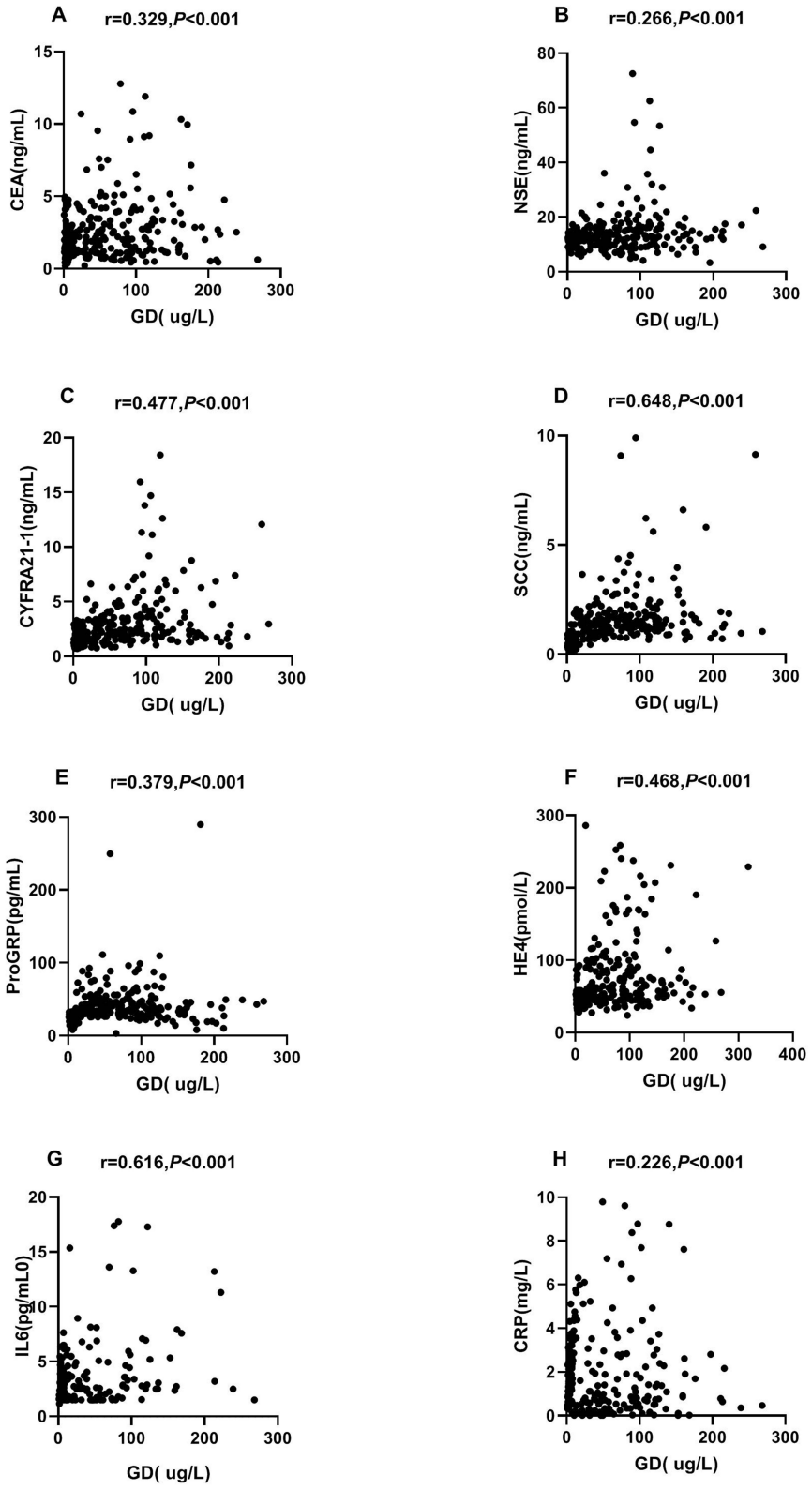

Figure 2 Analysis of the Correlation between plasma GSDMD and Markers of Tumor and Inflammation (**A**) scatterplot of plasma GSDMD levels associated with CEA;(**B**) scatterplot of plasma GSDMD levels associated with NSE;(**C**)catterplot of plasma GSDMD levels associated with CYFRA21-1;(**D**)catterplot of plasma GSDMD levels associated with SCC;(**E**)catterplot of plasma GSDMD levels associated with ProGRP;(**F**)catterplot of plasma GSDMD levels associated with HE4;(**G**)catterplot of plasma GSDMD levels associated with IL-6;(**H**)catterplot of plasma GSDMD levels associated with CRP.

Table 2 Correlation Between Serum GSDMD and Other Indicators (n=301)

Projects	GSDMD	
	r	*P Value*
CEA	0.329	0.000
NSE	0.266	0.000
CYFRA21-1	0.477	0.000
SCC	0.648	0.000
ProGRP	0.379	0.000
HE4	0.468	0.000
IL-6	0.616	0.000
CRP	0.226	0.000

Table 3 Logistic Regression Analysis of Serum GSDMD and Other Indicators in Lung Cancer

Independent Variable	Univariate		Multivariate	
	OR (95% CI)	*P Value*	OR (95% CI)	*P Value*
GD	1.024 (1.018~1.030)	<0.001	1.011(1.002~1.019)	0.012
CEA	1.689(1.416~2.016)	<0.001	1.315(1.058~1.635)	0.014
NSE	1.104(1.048~1.163)	<0.001	0.975(0.880~1.080)	0.625
CYFRA21-1	2.085(1.662~2.616)	<0.001	0.989(0.872~1.122)	0.862
SCC	4.160(2.727~6.346)	<0.001	1.869(1.057~3.305)	0.032
ProGRP	1.023(1.009~1.037)	0.001	1.009(0.995~1.023)	0.224
HE4	1.069(1.051~1.087)	<0.001	1.048(1.024~1.072)	0.000
IL-6	1.028(1.020~1.036)	<0.001	1.010(1.003~1.018)	0.007
CRP	1.106(1.061~1.152)	<0.001	1.005(0.979~1.032)	0.717

Table 4 ROC Curve Analysis of the Predictive Value of Serum GSDMD for the Occurrence of First Diagnosed Lung Cancer

Project	AUC	*P*	*95% CI*	Critical Value	Sensibility (%)	Specificity (%)
GSDMD	0.860	0.000	0.818~0.902	39.87	95.6	72.2
CEA	0.801	0.000	0.747~0.855	2.55	72.8	80.2
SCC	0.843	0.000	0.800~0.886	1.18	87.7	72.7
HE4	0.901	0.000	0.865~0.936	60.30	83.3	84.5
GD+CEA+SCC+HE4	0.959	0.000	0.941~0.977	–	93.0	82.9

Discussion

This study meticulously explored the role of serum Gasdermin D (GSDMD) in lung cancer, offering profound insights into its potential as a biomarker and its implications within the disease's intricate pathophysiology.

GSDMD is a pivotal protein in the pyroptosis pathway, a distinct form of programmed cell death that differs from apoptosis. Structurally, it is composed of an N - terminal effector domain and a C - terminal inhibitory domain. Under normal physiological conditions, the C - terminal domain acts as a safeguard, maintaining the N - terminal domain in an inactive state. However, upon activation by specific caspases, a significant transformation occurs. In the canonical

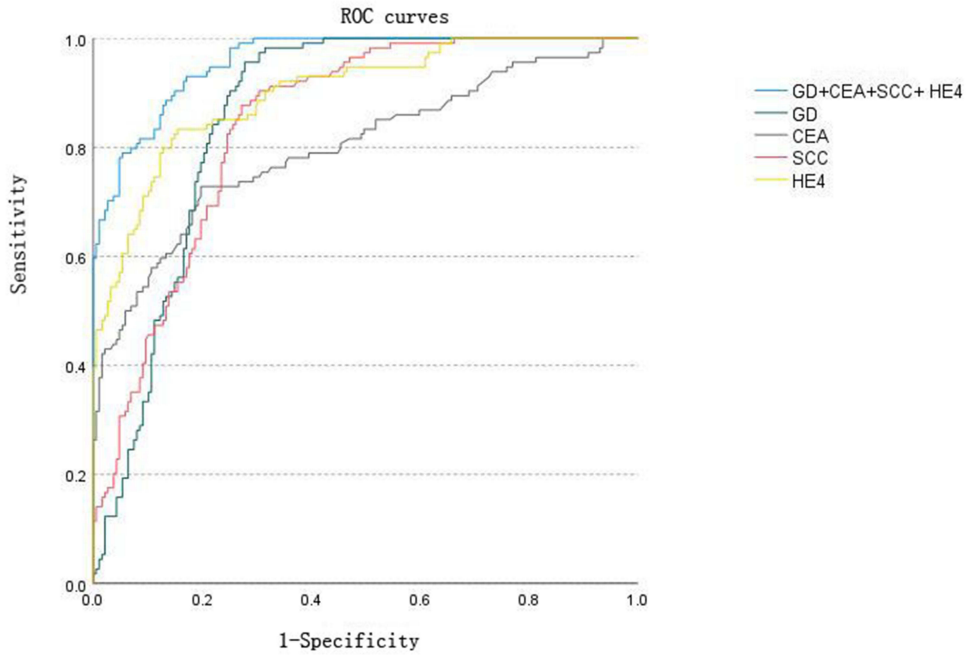

Figure 3 Predictive value of plasma GSDMD for Lung cancer ROC curve.

inflammasome pathway, caspase - 1 plays a crucial role in cleaving GSDMD. In the non - canonical pathway, caspases like caspase - 3/7 are responsible for this cleavage event. Once cleaved, the N - terminal fragment of GSDMD undergoes a series of remarkable changes. It translocates to the cell membrane, where it oligomerizes, forming pores that are approximately 10–14 nm in diameter. These pores are not just simple openings; they are gateways for the release of pro - inflammatory cytokines, such as interleukin - 1β (IL - 1β) and interleukin - 18 (IL - 18). The release of these cytokines triggers a cascade of immune responses, leading to an inflammatory reaction that can have far - reaching consequences.[13]

In the context of lung cancer, the function of GSDMD is a double - edged sword. On one hand, the induction of pyroptosis can be seen as a defense mechanism against cancer cells. By promoting cell death, GSDMD - mediated pyroptosis has the potential to halt the uncontrolled growth and spread of lung cancer cells. This is particularly important as lung cancer cells often exhibit abnormal growth patterns and resistance to traditional apoptosis. Pyroptosis offers an alternative route to eliminate these cancer cells, potentially reducing tumor burden. For example, there is emerging research evidence indicating that pyroptosis has the potential to suppress tumor growth and reverse drug resistance in cancer cells.[14] On the other hand, the release of pro - inflammatory cytokines as a result of GSDMD activation can also create an environment that is conducive to tumorigenesis. Chronic inflammation has long been recognized as a key driver in the development and progression of cancer. In the lung, this inflammatory microenvironment can promote angiogenesis, the formation of new blood vessels that supply nutrients to the growing tumor. It can also stimulate tumor cell proliferation, enabling cancer cells to multiply at an accelerated rate. Additionally, the inflammatory cytokines can facilitate metastasis, allowing cancer cells to break away from the primary tumor and spread to other parts of the body.[15] Therefore, understanding the delicate balance between the cell - killing and inflammatory - promoting functions of GSDMD in lung cancer is of utmost importance.

Our study, as vividly presented in Table 1, clearly showcases significant differences in serum GSDMD levels among the lung cancer group (LC), pulmonary nodule group (PN), and healthy control group (HC). The LC group had the highest GSDMD levels, with a median value of 94.05 pg/mL (interquartile range: 65.21–124.21 pg/mL), followed by the PN group with a median of 51.67 pg/mL (interquartile range: 30.25–96.69 pg/mL), while the HC group had the lowest levels, with a median of 5.06 pg/mL (interquartile range: 2.98–7.17 pg/mL). This distinct difference in levels indicates that GSDMD could potentially serve as a valuable biomarker for differentiating between lung cancer patients, those with pulmonary nodules (which may be pre - cancerous or benign), and healthy individuals.Similar trends were observed for

other well - known biomarkers such as CEA, NSE, and CYFRA21 - 1. For instance, CEA levels were significantly higher in the LC group compared to the PN and HC groups. This parallel behavior among multiple biomarkers further validates the reliability of GSDMD as a potential biomarker in this context. By measuring GSDMD levels in serum, clinicians may be able to identify individuals at a higher risk of lung cancer or detect the disease at an earlier stage. In a clinical setting, this could lead to more timely interventions and potentially better patient outcomes.

Table 2 demonstrates significant positive correlations between serum GSDMD and various other biomarkers. The strong correlation with IL - 6, with a correlation coefficient (r) of 0.616 and a P - value < 0.000, suggests that GSDMD may be intricately involved in the inflammatory processes associated with lung cancer. Inflammatory cytokines play a crucial role in tumor development, and the correlation with IL - 6 implies that GSDMD could be part of a complex network of molecules driving the disease progression. IL - 6 is known to activate various signaling pathways, including the STAT3 pathway, which can promote tumor cell survival, proliferation, and invasion.[16] The fact that GSDMD is correlated with IL - 6 suggests that they may act in concert to influence the development and progression of lung cancer. The correlations with tumor - associated antigens like CEA and SCC also suggest that GSDMD may share common regulatory pathways with these established biomarkers. CEA is a widely used biomarker for lung cancer, and its correlation with GSDMD indicates that there may be underlying molecular mechanisms that link the two. Similarly, SCC, which is often elevated in squamous cell carcinoma of the lung, shows a strong positive correlation with GSDMD. These correlations further highlight the potential of GSDMD as a valuable biomarker for lung cancer diagnosis and prognosis. By understanding these relationships, researchers may be able to develop more comprehensive biomarker panels that can provide a more accurate assessment of a patient's disease status. The logistic regression analysis in Table 3 reveals that GSDMD is an independent predictor of lung cancer. In the univariate analysis, all investigated variables, including GSDMD, CEA, NSE, CYFRA21 - 1, SCC, ProGRP, HE4, IL - 6, and CRP, were significantly associated with lung cancer. However, in the multivariate analysis, which takes into account the potential confounding effects of other variables, GSDMD, along with CEA, SCC, HE4, and IL - 6, remained significantly associated with the risk of lung cancer.GSDMD had an odds ratio (OR) of 1.011 (95% confidence interval: 1.002–1.019) with a P - value of 0.012 in the multivariate analysis. This indicates that for every unit increase in GSDMD levels, the odds of having lung cancer increase by 1.011 times, independent of the other variables in the model. The independent predictive value of GSDMD suggests that it could be used in combination with other biomarkers to improve the accuracy of lung cancer risk assessment. In current clinical practice, relying on a single biomarker may not be sufficient to accurately predict the risk of lung cancer. By incorporating GSDMD into a panel of biomarkers, clinicians can potentially obtain a more comprehensive and accurate picture of a patient's risk. This is particularly important as early detection of lung cancer is crucial for improving patient survival rates. Lung cancer is often diagnosed at an advanced stage, when treatment options are limited. Having reliable predictors like GSDMD can aid in more targeted screening and early intervention strategies, potentially saving lives.

The ROC curve analysis in Table 4 shows that serum GSDMD has a good predictive value for lung cancer, with an area under the curve (AUC) of 0.860. A value of 0.860 indicates that GSDMD can effectively distinguish between lung cancer patients and healthy controls.When combined with other biomarkers (CEA, SCC, and HE4), the predictive accuracy significantly improves, achieving an AUC of 0.959. This is in line with previous research demonstrating that multi - biomarker panels are more effective in predicting lung cancer than single biomarkers.[17] The combination of these biomarkers provides a more comprehensive assessment of a patient's disease status, taking into account different aspects of tumor biology.The high sensitivity and specificity values associated with GSDMD and the biomarker combination further support its potential use in clinical practice for the early detection of lung cancer. GSDMD had a sensitivity of 95.6% and a specificity of 72.2% at a critical value of 39.87 pg/mL. The combination of GSDMD, CEA, SCC, and HE4 had a sensitivity of 93.0% and a specificity of 82.9%. These values suggest that the biomarkers can accurately identify a large proportion of true positive cases while minimizing the number of false positive cases.

Our findings are consistent with several previous studies. High expression of GSDMD is associated with aggressive features, including larger tumor size and later tumor-node-metastasis (TNM) staging. Additionally, high expression of GSDMD in lung cancer predicts poor prognosis. Analysis revealed a correlation between GSDMD and

EGFR/Akt signaling. GSDMD knockout weakened tumor proliferation by promoting NSCLC cell apoptosis and inhibiting EGFR/Akt signaling transduction. In summary, GSDMD is an independent prognostic biomarker for LUAD.[18] Emerging evidence has established a correlative relationship between GSDMD and inflammatory cytokine dysregulation in pulmonary pathologies. In asthmatic patients, immunohistochemical analyses reveal markedly elevated expression of the activated N-terminal fragment of GSDMD (N-GSDMD) within airway epithelial compartments, a phenomenon observed to colocalize with heightened concentrations of the pro-inflammatory interleukins IL-1β and IL-18.[19] Furthermore, mechanistic investigations in chronic obstructive pulmonary disease (COPD) models demonstrate that GSDMD-mediated pyroptosis contributes to disease pathogenesis via the NLRP3/caspase-1/GSDMD signaling axis, thereby amplifying inflammatory cascades through programmed cell death mechanisms. This consistency across studies further validates the relationship between GSDMD and inflammation in the context of lung diseases, including lung cancer.[20] In addition, the use of logistic regression and ROC curve analysis to assess the significance and predictive value of the biomarkers in our study is in line with the standard practice of biomarker studies and adds credibility to the findings. Regarding cost, GSDMD detection (eg, ELISA-based) shows advantages with lower equipment investment and per-test costs, compared to LDCT.For turnaround time, GSDMD assays (4–12 hours for serum/tissue) are faster than LDCT (2–4 days, limited by scheduling and image review).In comparison with LDCT, GSDMD serves as a complementary molecular marker: while LDCT excels in anatomical visualization, GSDMD aids in distinguishing benign/malignant lesions and monitoring disease activity, with no radiation risk.

While this study provides valuable insights into the role of GSDMD in lung cancer, there are several limitations that should be acknowledged. First, the study was conducted in a single center with a relatively small sample size. Larger, multi-center studies are needed to validate these findings and to explore the potential of GSDMD as a diagnostic and therapeutic target in lung cancer. Second, the study did not investigate the molecular mechanisms underlying the elevated levels of GSDMD in lung cancer. Future research should focus on elucidating the role of GSDMD in lung cancer pathogenesis, particularly its involvement in pyroptosis and inflammation.

In conclusion, this study provides strong evidence for the research value of GSDMD in lung cancer. Its unique structure and function place it at the intersection of cell death and inflammation, making it a potential target for therapeutic intervention. In addition, as a biomarker, whether used alone or in combination with other markers, it offers great hope for distinguishing between benign and malignant lung diseases and improving the diagnosis and prognosis of lung cancer.However, further research is needed to fully understand the complex mechanisms by which GSDMD influences lung cancer development and progression, and to translate these findings into clinical applications. Future studies could focus on exploring the upstream and downstream regulators of GSDMD in lung cancer, as well as developing targeted therapies that can modulate its function to benefit patients.

Data Sharing Statement

All data are available in the main text. Upon reasonable request, the corresponding author can provide anonymized clinical data supporting the results of this study.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, received approval from the Ethics Committee of Hebei General Hospital [Approval Number:2024(288)], and all participants provided informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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