Available Online: 8 April 2026 DOI: 10.54254/3049-5458/2026.32736

ABC transporters in lung cancer clinical outcome: a systematic review and integrative analysis

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Abstract. Drug resistance represents a significant factor contributing to poor patient survival and prognosis in lung cancer, frequently mediated by ATP-Binding Cassette (ABC) transporters. This systematic review synthesizes clinical studies, in vitro and in vivo experimental research published between January 2000 and March 2025 in the PubMed and Web of Science databases, alongside analyses of untreated lung cancer cohorts from The Cancer Genome Atlas (TCGA) accessed through the cBioPortal platform. The goal of this review is to evaluate the association between ABC transporter expression, treatment response, drug resistance, and patient survival. Clinical studies have demonstrated considerable heterogeneity in the association between ABC transporter levels in cancer patients and their chemotherapy outcomes. In contrast, non-clinical studies have shown greater consistency in evaluating the roles of certain ABC transporters in drug resistance and tumor progression. Analysis of TCGA data showed that most ABC genes were not intrinsically associated with survival. Overall, our findings indicate that ABC transporters influence lung cancer progression primarily through drug efflux–mediated mechanisms, with limited evidence for intrinsic survival effects in untreated disease. The observed heterogeneity across clinical studies highlights the need for standardized analytical approaches and treatment-specific regimens.

Keywords: ABC transporter, drug resistance, lung cancer, clinical outcomes, overall survival

1. Introduction

Lung cancer remains one of the most prevalent cancers worldwide and is responsible for the highest death rate among all cancer-related deaths [1]. According to data from 2022, lung cancer caused around 2.48 million of newly diagnosed cases and 1.8 million deaths globally [1-3]. In the United States, the mortality rate of lung cancer reached 30.2 per 100,000 persons in 2022 [3]. The elevated mortality rate associated with lung cancer primarily results from late-stage diagnosis, as more than 50% of patients are diagnosed with metastatic disease [3]. As a result, they must receive systemic chemotherapy, even after surgical resection of cancer tissue [3, 4]. Non-Small Cell Lung Cancer (NSCLC) occupies the majority of lung cancer diagnoses, whereas Small Cell Lung Cancer (SCLC) occurs less frequently [5]. Drug treatment in both types is often hampered by intrinsic or acquired drug resistance, which manifests as lower response rates and decreased Overall Survival (OS) [6, 7]. NSCLC is generally categorized into Lung Adenocarcinoma (LUAD) and Lung Squamous Cell Carcinoma (LUSC) [8]. LUAD cells originate from the pulmonary epithelium in the lung parenchyma, while LUSC cells

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originate from the basal cells of the respiratory airways [9]. Although both types are typically treated with the similar chemotherapy regimens clinically, they differ in their mutated genes, therapeutic targets, and causative factors. Common mutations found in patients of LUAD include KRAS, EGFR, ALK, and BRAF, while common mutations found in patients of LUSC include FGFR1, PIK3CA, and DDR2 [9]. Furthermore, LUAD occurs more frequently in non-smokers, whereas LUSC is linked to a history of smoking [8].

One major contributor to treatment failure is Multidrug Resistance (MDR). Once cancer cells develop resistance against a specific drug, they can also acquire resistance against other type of drugs that are structurally and mechanistically unrelated [10]. Multidrug Resistance (MDR) is primarily caused by a group of membrane proteins within the ATP-Binding Cassette (ABC) transporter superfamily. These transporters decrease intracellular drug accumulation via active efflux, which reduces the effective concentration of cytotoxic agents at their intracellular targets [4, 5, 10]. The most extensively studied MDR-related transporters include ABCB1 (P-glycoprotein/MDR1), ABCC1 (MRP1), and ABCG2 (BCRP), all of which can export structurally diverse anticancer drugs and contribute to drug resistance in various tumor types [11-14]. Furthermore, these transporters can be found in a wide variety of human tissues, including the small intestines, large intestines, lungs, liver, kidneys, and brain, making them to be crucial in multidrug resistance within many cancer types [15-18]. However, the clinical significance of ABC transporter expression in lung cancer patients is not yet well defined. Many commonly used lung cancer targeted chemical drugs like cisplatin, paclitaxel, gemcitabine, and pemetrexed have been explored as substrates of those transporters [5, 19, 20]. Besides drug efflux, increasing evidence suggests that ABC transporters can influence cancer biology through other mechanisms, such as regulating apoptosis, lipid transport, migration & invasion, etc. [21]. Notably, some ABC transporters have been reported to suppress tumor cell proliferation and have a relationship with improved lung cancer patients' clinical outcomes [22, 23]. These characteristics further complicated the association between ABC transporter expression and patients' clinical outcomes.

Numerous researchers have conducted clinical observational studies to examine the association between specific ABC gene expression in lung cancer patients and clinical outcomes, including Overall Survival (OS), Progression-Free Survival (PFS), and Disease-Free Survival (DFS). However, due to cancer heterogeneity, limited patient sample sizes, and differences in chemotherapeutic regimens across studies, discrepancies arise [24-26]. These discrepancies complicate the question of whether ABC transporter expression can be considered a predictive biomarker of chemotherapy efficacy or a mechanistic clue to guide strategies to overcome drug resistance.

To further evaluate the ABC transporter gene's importance in lung cancer and provide a comprehensive overview of current research findings, this review systematically investigated peer-reviewed evidence from January 2000 to March 2025, examining how changes in ABC transporter gene expression relate to (i) lung cancer prognosis and treatment response from clinical studies and database or (ii) drug resistance, including in vitro cell line models and animal studies. This review aims to clarify areas of convergence and discrepancy within the existing literature, and to identify ABC transporters that show the greatest promise for further validation as prognostic biomarkers or therapeutic targets.

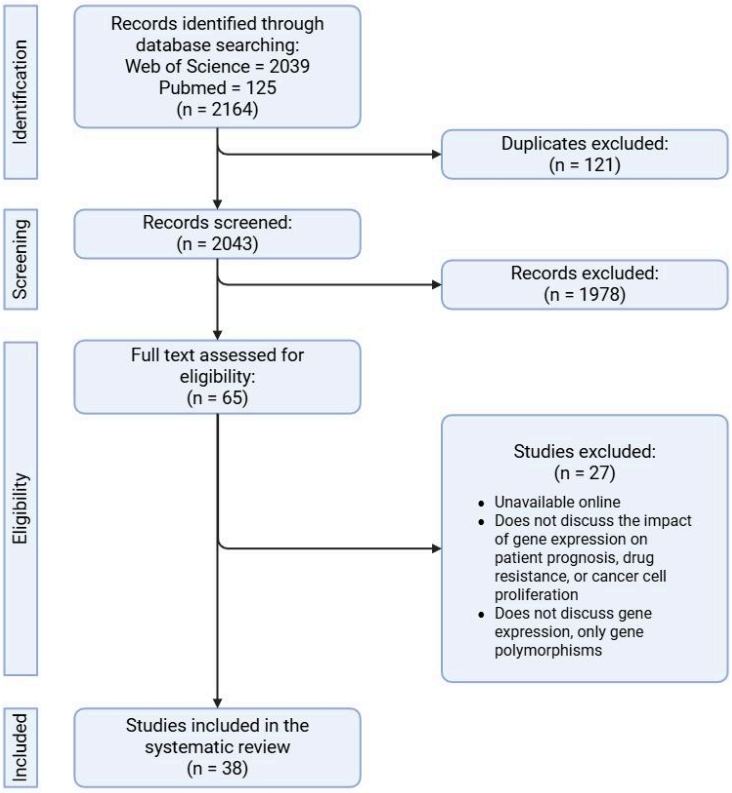

Figure 1. PRISMA flow diagram for article screening and inclusion

2. Methods

2.1. Search strategy

We searched the PubMed and Web of Science databases to identify available studies published between January 2000 and March 2025. The following search string was used:

(ATP-Binding Cassette Transporters OR ABC transporter OR ATP binding cassette OR multidrug resistance OR MDR OR ABCA3 OR ABCB1 OR MDR1 OR P-gp OR ABCG2 OR BCRP OR ABCC1 OR MRP1 OR ABCC2 OR MRP2) AND (Lung cancer OR lung carcinoma OR NSCLC OR SCLC OR non-small cell lung cancer OR small cell lung cancer) AND (expression OR gene expression OR expression level OR expression profile) AND (prognosis OR survival OR overall survival OR OS OR PFS OR DFS OR response OR drug resistance)

The search strategy aimed to identify studies examining the association between ABC transporter gene expression and clinical outcomes or therapeutic response in lung cancer. Additionally, the references of included articles were manually reviewed to locate further relevant studies.

2.2. Eligibility criteria

Studies were included or excluded based on the following criteria:

2.2.1. Inclusion criteria

The following articles were included: (1) the study population comprised human, animal, or cell line models related to lung cancer; (2) the study design was an adaptive clinical trial, clinical study, case report,

comparative study, cohort study, case–control study, cross-sectional study, evaluation study, multicenter study, observational study, or randomized controlled trial; (3) the study reported an association between ABC transporter gene expression and patient prognosis or drug response; (4) the study focused on lung cancer, including Non–Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC); (5) the article was a peer-reviewed, full-text original research article; and (6) the article was published in English.

2.2.2. Exclusion criteria

The following articles were excluded: (1) non-cancer populations or unrelated cancer types; (2) editorials, commentaries, conference abstracts without full data, or review articles; (3) the studies assessing only gene polymorphisms without measuring gene expression levels; (4) the studies without extractable or relevant data; (5) duplicate publications based on the same dataset or retrieved from multiple databases; (6) articles unavailable online or not published in English.

2.2.3. Study selection

All titles and abstracts identified from the database search were screened by a single reviewer to assess eligibility. Subsequently, full-text articles were assessed according to the previously specified inclusion and exclusion criteria. Any uncertainties about study eligibility were discussed with the project supervisor before a final decision was made.

2.3. Data extraction and management

Data from eligible studies were extracted by a single reviewer using a standardized table designed for this review. Extracted information included study details (authors, year, and publication link), gene names, cancer types, treatment and drug names, timing of data collection (before or after treatment), and outcomes. Outcomes were categorized as either "Agree" or "Disagree" with the review hypothesis, with additional notes summarizing the detailed results and authors' interpretations.

3. Results

Initially, 2,173 articles were identified; after removing duplicate articles from the database, 2,043 articles remained for screening. Following screening based on the inclusion and exclusion criteria, only 38 articles were included in this review (Figure 1).

3.1. Mechanistic features with substrates, cellular localization, tissue expression, cellular functions related to cancer

Several widely used lung cancer treatment drugs, including cisplatin, paclitaxel, and methotrexate, can be the substrate of various ABC transporters. This interaction results in reduced intracellular drug concentrations and diminished cytotoxic effects [27, 28]. However, while the most well-established role of ABC transporters in cancer is ATP-dependent drug efflux, their contribution to lung cancer treatment failure cannot be fully explained by efflux alone. Growing evidence suggests that ABC transporters can also regulate cancer biology through drug-independent functions, including regulation of proliferation, migration/invasion, and other cancer hallmarks [22]. For example, ABCA3 has been reported to regulate the migrating and invasive behavior in LUAD models, whereas ABCC1 relates to promotion of tumor cell proliferation and migration/invasion (Table 1) [13, 29]. Collectively, these pleiotropic functions indicate that the relationship between ABC transporter expression and clinical outcomes exceeds simple drug resistance models; therefore, understanding these associations requires consideration of ABC transporter substrates, localization, and function in cancer biology:

Table 1. Characterization of the ABC genes

ABC Gene	Other name(s)	Cellular function	Tissue expression	Cellular localization
ABCA2	N/A	Cholesterol sequestration. Cholesterol homeostasis. Sphingolipid catabolism [27]	Brain Ovary Leukocytes Macrophages	Late Endosomes/Lysosomes (LELs) Trans-Golgi Endoplasmic Reticulum (ER)
ABCA3	N/A	Phospholipids & cholesterol transportation [30].	Brain, Pancreas Skeletal muscle Heart Lung [31]	LELs [32], Outer membrane of lamellar bodies [30]
ABCB1	P-glycoprotein (P-gp) MDR1	Efflux pump [16].	Brain [15], Intestine Liver Kidney Blood–Brain Barrier Placenta Lymphocytes [16]	Nuclear envelope, caveolae, cytoplasmic vesicles, Golgi complex, rER [15]
ABCC1	MRP1	Export of organic anions and drugs [39].	Skeletal muscle Brain Heart Spleen Lung Kidney [17]	Plasma membrane Smooth membrane caveolae Clathrin-coated vesicles [39]
ABCC2	MRP2	ATP-dependent lipophilic compound transport.ATP-dependent transporter for Leukotriene C4 (LTC4) and 17β-glucuronosyl estradiol [41]	Liver [42]	Apical membrane [41]
ABCC3	MRP3	Transports organic anions.Transports the bile salts taurocholate, glycocholate, taurochenodeoxycholate 3-sulfate, and taurolithocholate-3-sulfate [45]	Adrenal glands Intra-hepatic bile ducts Small intestine Kidney Pancreas [45]	Basolateral membranes [45]
ABCC4	MOATBMRP4	Exports endogenous and xenobiotics from cells [47].	Widely in normal tissues [47]	Apical or basolateral membranes [47]
ABCC5	N/A	Endogenous metabolites transported include cyclic nucleotides, folic acid, and N-lactoyl-amino acids [49]	Ubiquitously expressed, high in brain and muscle [49]	Apical or basolateral membranes [49]
ABCC7	CFTR	Functions as a cAMP-activated, ATP-gated chloride channel and regulates cellular conductance.Also facilitates Glutathione (GSH) efflux [50].	Lungs Gastrointestinal tract Exocrine pancreas Sweat ducts [50]	Apical membrane [50]
ABCC11	MRP8	Exports physiological compounds and xenobiotics from cells [54].	Breast Testis Axons of the central and peripheral nervous system [55]	Plasma membrane Apical membrane [56]
ABCG2	BCRP	Cell protection against xenobiotic [18]	Placenta Intestine Liver Breast Renal proximal tubule Adrenal glands Stem cells Capillaries and veins [18]	Plasma membrane Apical membrane [18]
ABCG4	WHITE2	Efflux of sterols [61]	Brain Eye [62]	Plasma membrane [61]

Table 1. Continued

ABC Gene	Other name(s)	Drug substrates	Function in cancer biology
ABCA2	N/A	estramustine estradiol mitoxantrone [28]	Drug resistance [28], Increase metastasis/invasion [29]
ABCA3	N/A	phospholipids [33], mitoxantrone etoposide Ara-C vincristine doxorubicin cytarabine vinblastine epirubicin [34], vinca alkaloids cisplatin paclitaxel [35]	Inhibition of Epithelial-Mesenchymal Transition (EMT) process [36], Drug resistance [35], Against endogenous defense mechanisms [37]
ABCB1	P-glycoprotein (P-gp) MDR1	doxorubicin etoposide imatinib paclitaxel teniposide vinblastine vincristine [16], Amrubicin [38]	Drug resistance [16]
ABCC1	MRP1	vincristine doxorubicin, flavonoids daunorubicin imatinib methotrexate [40]	Drug resistance [17], Increase proliferationIncrease migrationMacrophage infiltration [13]
ABCC2	MRP2	etoposide vincristine cisplatin doxorubicin epirubicin [41], vinblastine [43]	Drug resistance [41], Inducing metabolic vulnerability and ferroptosis in cancer through enhanced glutathione efflux [43]. Improve Tregs infiltration into tumor [44]
ABCC3	MRP3	methotrexate vincristine doxorubicin etoposide cisplatin [45]	Drug resistance [45], Cancer cell glycolytic abilityIncrease proliferation [46]
ABCC4	MOATBMRP4	nucleobase analogsnucleotide analogsnucleoside analogs [47] *There is currently no clear relationship between ABCC4 and drug resistance in lung cancer.	Drug resistanceIncrease EMT processIncrease proliferation [48]
ABCC5	N/A	nucleotide analogs antifolates like [49], Gemcitabine [19], doxorubicin pemetrexed vincristine enzalutamide paclitaxel [20]	Drug resistance [20]
ABCC7	CFTR	small inorganic anions drugs [51]	Suppresses NFκB activity, Controlling EMT process [52], Inhibit progression [53]
ABCC11	MRP8	methotrexate5-FU [54], alectinib [57], methotrexate [58]	Drug resistance [58], Increase metastasis, Venous invasion [59]
ABCG2	BCRP	mitoxantrone camptothecin derivates flavopiridol methotrexate imatinib gefitinib nilotinib prazosin glyburide cimetidine sulfasalazine rosuvastatin [60]	Protecting cells from oxidative damage, Drug resistance [60]
ABCG4	WHITE2	alkyl-phospholipid analogues [63], doxorubicin [64]	Drug resistance [63]

Table 1 shows the aliases, cellular functions, expression, subcellular localization, drug substrates, and cancer biological functions of 12 ABC transporters. The table aims to provide mechanistic context for interpreting associations reported in clinical treatment cohorts, in vitro experimental drug resistance models, and cancer prognostic analyses.

3.2. ABC transporter expression and chemotherapy response in treated lung cancer cohort

The association between the level of eight ABC genes and responses to chemotherapy and radiotherapy, as well as related clinical outcomes, has been examined in clinical studies (Table 2). These genes are ABCA3, ABCB1, ABCC1, ABCC2, ABCC3, ABCC4, ABCG2, and ABCG4. Among them, ABCB1, ABCC1, and ABCG2 are the most widely studied and discussed genes and are frequently associated with poor clinical outcomes.

Table 2. ABC gene expression in clinical trials with clinical outcomes

Study	ABC gene(s)	Cancer type	Sample size	Treatment / Intervention	Timing of data collection
Overbeck et al. [38]	ABCA3	LUAD, LUSC	89	chemotherapy (28 patients), radiotherapy (14 patients), None (47 patients)	Pre and After-treatment
Zhao et al. [27]	ABCC3	LUAD, LUSC, Other	199	None	N/A
Yue et al. [24]	ABCC4	LUAD, LUSC	30	N/A	N/A
Jeleń et al. [74]	ABCG2	LUAD, LUSC	50	Chemotherapy (50 patients)	N/A
Li et al. [70]	ABCC1, ABCG2,	LUAD, LUSC	46	vinorelbine + cisplatin (27 patients), gemcitabine + cisplatin (19 patients).	Pre-treatment
Yoh et al. [25]	ABCB1, ABCC1, ABCC2, ABCC3, ABCG2	LUAD, LUSC Large-Cell Carcinoma (LCC)	72	vinorelbine + cisplatin (25 patients), docetaxel + cisplatin (16 patients), irinotecan + cisplatin (11 patients), gemcitabine + cisplatin (10 patients), paclitaxel + carboplatin (10 patients).	Pre-treatment
Chiou et al. [67]	ABCB1	LUAD, LUSC	40	paclitaxel + cisplatin (40 patients)	Pre-treatment
Li et al. [26]	ABCC1, ABCG2	LUAD, LUSC	60	vinorelbine + cisplatin (38 patients), gemcitabine + cisplatin (22 patients).	Pre-treatment
Yang et al. [64]	ABCG4	LUAD, LUSC	140	gemcitabine + cisplatin pemetrexed + cisplatin docetaxel + cisplatin	Pre-treatment
Ota et al. [72]	ABCC2, ABCG2	LUAD, Non-LUAD	156	vinorelbine + cisplatin (68 patients), docetaxel + cisplatin (20 patients), irinotecan + cisplatin (16 patients), gemcitabine + cisplatin (15 patients), paclitaxel + carboplatin (28 patients).	Pre-treatment
Berger et al. [23]	ABCB1, ABCC1	LUAD, LUSC, Bronchioloalveolar Carcinoma (BAC), LCC	126	Chemotherapy (36 patients), EPICO treatment (4 patients), None (77 patients)	Pre and After-treatment
Yeh et al. [7]	ABCB1	LUAD, LUSC	50	paclitaxel+ cisplatin (50 patients)	Pre-treatment
Fang et al. [71]	ABCC1	LUAD, LUSC	427	None	N/A
Zou et al. [11]	ABCB1	LUAD	194	N/A	N/A

Table 2. Continued

Maraz et al. [84]	ABCB1	LUAD, LUSC	32	During the radiotherapy, all the patients received concomitant taxane-based chemotherapy.Among the 19 stage IIIB patients who completed one or two cycles of induction chemotherapy, 17 received a taxane-based regimen and 2 received a gemcitabine-based regimen. Following chemoradiotherapy, 18 patients received additional consolidation chemotherapy with either paclitaxel plus carboplatin or docetaxel plus CDDP.	Pre-treatment
Li et al. [70]	ABCG2	LUAD, LUSC	145	None	N/A
Triller et al. [68]	ABCB1, ABCC1	SCLC	17	cisplatin/etoposide based regimen (17 patients)	Pre and After-treatment
Rijavec et al. [66]	ABCB1, ABCC1, ABCG2	SCLC	21	cisplatin/etoposide and/or cyclophosphamide/epirubin (doxorubicin)/vincristine (21 patients)	Pre-treatment
Yeh et al. [69]	ABCB1, ABCC1	SCLC	40	cisplatin and etoposide (40 patients)	Pre-treatment

Table 2. Continued

Study	ABC gene(s)	Cancer type	Sample size	Outcome(s)	Main findings
Overbeck et al. [38]	ABCA3	LUAD, LUSC	89	overall survival, disease-free survival	ABCA3 positivity correlates with reduced overall survival.ABCA3 positivity correlates with reduced disease-free survival.
Zhao et al. [27]	ABCC3	LUAD, LUSC, Other	199	overall survival	ABCC3 positivity correlates with shorter overall survival.
Yue et al. [24]	ABCC4	LUAD, LUSC	30	overall survival	High expression of ABCC4 was not correlated with shorter overall survival.
Jeleń et al. [74]	ABCG2	LUAD, LUSC	50	overall survival, first-progression survival, post-progression survival	High expression of ABCG2 in LUAD patients was correlated with improved OS and FP.High expression of ABCG2 in LUSC patients was correlated with poorer FP and PPS.High ABCG2 expression was significantly correlated to better OS and FP in overall lung cancer patients.
Li et al. [70]	ABCC1, ABCG2,	LUAD, LUSC	46	overall survival, tumor-free survival	Patients with low ABCC1 expression had significantly longer TFS than those with high ABCC1 expression.Patients with low ABCC1 expression had significantly longer OS than those with high ABCC1 expression.Prechemotherapy ABCG2 expression did not correlate with response to cisplatin-based chemotherapy or patient survival.

Table 2. Continued

Yoh et al. [25]	ABCB1, ABCC1, ABCC2, ABCC3, ABCG2	LUAD, LUSC Large-Cell Carcinoma (LCC)	72	overall survival, progression-free survival, response rate	No significant associations were found among expressions of ABCB1, ABCC1, or ABCC3, and either response to chemotherapy or survival. A higher expression of ABCC2 expression was associated with poorer overall survival.ABCG2 positivity was associated with a shorter PFS and overall survival.
Chiou et al. [67]	ABCB1	LUAD, LUSC	40	response rate	ABCB1 positivity is associated with poorer response rate.
Li et al. [26]	ABCC1, ABCG2	LUAD, LUSC	60	overall survival, tumor-free survival	A higher expression of ABCC1 was correlated with a poorer TFS. The expression level of ABCG2 was not significantly associated to TFS. A high expression levels of ABCC1 were associated with a poor overall survival. ABCG2 expression levels did not show a significant association with overall survival.
Yang et al. [64]	ABCG4	LUAD, LUSC	140	overall survival	ABCG4 positivity is associated with shorter overall survival.
Ota et al. [72]	ABCC2, ABCG2	LUAD, Non-LUAD	156	overall survival, progression-free survival, response rate	No significant associations were found between ABCC2 expression and response to chemotherapy, PFS, or overall survival.ABCG2 expression was significantly associated with shorter PFS and overall survival, but was not linked to chemotherapy response.
Berger et al. [23]	ABCB1, ABCC1	LUAD, LUSC, Bronchioloalveolar Carcinoma (BAC), LCC	126	overall survival,	No significant associations were found between ABCB1 expression and overall survival. A higher ABCC1 expression was associated with a better overall survival. (Relationship more pronounced when only untreated NSCLC patients were included.)
Yeh et al. [7]	ABCB1	LUAD, LUSC	50	response rate	ABCB1 positivity is associated with poorer response rate.
Fang et al. [71]	ABCC1	LUAD, LUSC	427	overall survival, diseasefree survival	ABCC1 expression was not associated with OS.ABCC1 expression was not associated with DFS.
Zou et al. [11]	ABCB1	LUAD	194	overall survival, diseasefree survival	ABCB1 positivity in stage I LUAD patients was significantly associated with poorer survival. No significant association was found when considering stage I-III as a whole.ABCB1 positivity in stage I patients has shown a worse DFS trend (difference was not statistically significant).
Maraz et al. [84]	ABCB1	LUAD, LUSC	32	overall survival, progression-free survival	A higher expression of ABCB1 was significantly associated with a poorer PFS.A higher expression of ABCB1 was significantly associated with a poor response rate.
Li et al. [70]	ABCG2	LUAD, LUSC	145	recurrence-free survival	ABCG2 expression was not related to recurrence-free survival.

Table 2. Continued

Triller et al. [68]	ABCB1, ABCC1	SCLC	17	response rate	ABCB1 positivity correlates with a lower response rate.ABCC1 positivity correlates with a lower response rate.
Rijavec et al. [66]	ABCB1, ABCC1, ABCG2	SCLC	21	overall survival	ABCB1 expression was not associated with the overall survival in SCLC patients.ABCC1 expression was not associated with overall survival in SCLC patients.A higher expression levels of ABCG2 were associated with poor overall survival.
Yeh et al. [69]	ABCB1, ABCC1	SCLC	40	response rate	ABCB1 positivity is linked to a lower response rate.ABCC1 positivity is linked to a lower response rate.

Table 2 shows clinical studies on the association between ABC transporter expression and lung cancer outcomes. This table summarizes clinical studies that measured ABC transporter expression in patient-derived lung cancer samples and its association with treatment response and survival in NSCLC and SCLC patients with or without chemotherapy. For each study, the sample size, treatment regimen, time of biological sample collection, clinical endpoint outcomes, and key findings are listed.

Multiple clinical trials have demonstrated that ABCB1 gene level is not related with Overall Survival (OS) across various cancer types [11, 23, 25, 65]. However, when considering only the response rate to chemotherapy, elevated ABCB1 expression is typically associated with poorer treatment outcomes [7, 66-68]. This difference may stem from differences in the chemotherapeutic regimens received by patients across and within studies [25]. Interestingly, Zou at 2017 also found that elevated ABCB1 expression was significantly related with decreased OS in stage I (p = 0.03), but this significance disappeared when the entire range of stages I-III was included [11]. These findings indicate that ABCB1 expression likely has a more important role during the initial stages of cancer.

The clinical manifestations of the ABCC1 gene are more heterogeneous. Four studies indicate that high ABCC1 expression is significantly related with reduced overall survival and lower chemotherapy response rates in both NSCLC and SCLC patients [26, 67-69]. However, a 2005 study by Berger et al. reported contrasting associations. Specifically, high ABCC1 expression was linked to longer overall survival, with the association being even more pronounced among untreated NSCLC patients [23]. Besides, three studies couldn't find any significant associations between ABCC1 expression and OS despite cancer types [25, 65, 70]. This discrepancy suggesting that the prognostic association of ABCC1 may depend on different experimental detective methodologies and sample types.

Clinical outcomes of ABCG2 show heterogeneity across treatment cohorts. Among patients who has Non-Small Cell Lung Cancer (NSCLC) and obtained a platinum-based regimen of chemotherapy, two studies indicated no observed relationship between ABCG2 expression and clinical outcomes [26, 69]. However, two other studies found that elevated ABCG2 expression was related with shorter PFS and OS [25, 71]. Notably, the two studies reporting a negative correlation both included patients receiving five different platinum-based regimens: vinorelbine, docetaxel, irinotecan, gemcitabine, and paclitaxel. In contrast, the two studies that found no association included only regimens containing vinorelbine and gemcitabine. This may suggest that ABCG2 exhibits differential substrate specificity for various chemotherapeutic drugs. Another study involving an untreated NSCLC cohort reported that there was no observable relation between ABCG2 expression and recurrence-free survival [72]. Separate analyses of clinical endpoints in LUAD and LUSC patients demonstrated that elevated ABCG2 expression associated with longer overall survival and first-progression

survival in LUAD patients, whereas it was associated with shorter first-progression and post-progression survival in LUSC patients [73]. ABCG2 expression was also linked to improved overall survival in patients with lung cancer [73]. This may indicate that ABCG2's prognostic role depends on lung cancer subtype.

3.3. In vitro/vivo evidence supporting ABC transporter related drug resistance

Table 3. In vitro and in vivo evidence of ABC transporter related drug resistance in lung cancer

Study	ABC gene(s)	Cancer type	Model used	Drug(s) tested
Song et al. [29]	ABCA3	LUAD	A549 cells	N/A
Zhao et al. [27]	ABCC3	LUAD, LUSC, Other	primary cancer cells	paclitaxel, docetaxel, gemcitabine, vinorelbine, cisplatin
Yue et al. [24]	ABCC4	LUAD, Giant Cell Carcinoma (GCC)	A2, L, 801D, H446, H460, 95C, H1299, A549, MRC-5 cells	N/A
Funazo et al. [59]	ABCC11	LUAD	KTOR1 and KTOR1-RE cells, NCI-H2228 cellsSix-week-old female BALB/c-nu mice	alectinib
Meng et al. [75]	ABCB1	LUAD, LUSC, Large-Cell Carcinoma (LCC)	NCI-H460, A549, SK-MES-1, LTEP-a-2, SPC-A-1, QG56, 95D, 95C, Anip973, GLC-82, AGZY83a, BH-1, LH7, L18, PAa, PG, HB-99 cells	paclitaxel
Xiao et al. [54]	ABCC7	LUAD	Calu-3 HBT-55 cells	N/A
Galetti et al. [78]	ABCG2	LUAD, LUSC	HCC827, H292, H460, H1299 A549, Calu-1, SKMES-1, SKLU-1	gefitinib
Yabuki et al. [76]	ABCB1	LCC	NCI-H460	paclitaxel
Han et al. [77]	ABCB1, ABCC1	LUAD, LUSC, Other	primary cancer cells	N/A
Chen et al. [85]	ABCC2	LUAD	A549, Male BALB/c nude mice (4 weeks old)	cisplatin
Oguri et al. [19]	ABCC5	LUAD, LUSC, Large-Cell Carcinoma (LCC)	A549, NCI-H23, PC-9, PC-14, VMRC-LCD, VMRC-LCF, RERF-LC-MT, RERF-LC-OK, RERF-LC-MS, NCU-LC-201, ACC-LC-94, ACC-LC-176, and SK-LC-10PC10 and QG56NCI-H460 and SK-LC-6	gemcitabine
Overbeck et al. [38]	ABCA3	LUADSCLC	NSCLCA549, NCI-H1650, NCI-H1975SCLCNCI-H69	cisplatin paclitaxel vinorelbine
Uemura et al. [28]	ABCC11	SCLC	PC-6 cells	methotrexate
Omori et al. [12]	ABCB1, ABCG2	SCLC	SBC-3, SBC-5, H69, H69AR, H719, H1048, H1105, H1417, DMS53, H1882, MS-1, Lu-139.	etoposideSN-38
Boonstra et al. [31]	ABCA2	SCLC	GLC4	estramustine mitoxantrone
Takakuwa et al. [40]	ABCB1	SCLC	PC-6	Amrubicin

Table 3. Continued

Study	ABC gene(s)	Cancer type	Method of data collection	Result
Song et al. [29]	ABCA3	LUAD	Cell proliferation (MTT assay), Cell migration (Wound healing assay), Cell invasion (Transwell assay)	Following siRNA transfection, A549 cell proliferation was enhanced.The wound healing rate in ABCA3-knockdown (ABCA3-KD) cells exceeded that observed in normal A549 cells.Transwell assay showed that the invasion of ABCA3-Knockdown cells was significantly enhanced after transfection.
Zhao et al. [27]	ABCC3	LUAD, LUSC, Other	Drug response (MTT assay), Gene expression (real time-PCR)	ABCC3 mRNA levels were higher in the resistant group than in the sensitive group across all five drugs.
Yue et al. [24]	ABCC4	LUAD, Giant Cell Carcinoma (GCC)	Cell proliferation (MTS assay), Gene expression (real time-PCR), Colony formation, Cell cycle analysis (flow cytometry), Protein detection (Western blot)	ABCC4 was highly expressed in most lung cancer cell lines compared with normal human fetal lung fibroblasts cell line.ABCC4 KD suppressed the growth rate and colony-forming efficiency of cancer cells.ABCC4 KD cells exhibited a reduced percentage of cells entering S phase, accompanied by an increased population in the G0/G1 phase.Phosphorylation of the pRB S780 protein was weakened when ABCC4 expression was inhibited.
Funazo et al. [59]	ABCC11	LUAD	Drug response (CellTiter-Glo 2.0), Gene expression (real time-PCR), Intracellular drug conc. (HPLC–MS/MS), Xenograft models (mice)	ABCC11 gene expression was significantly elevated in drug-resistant cells.Knockdown of ABCC11 reduced cell viability in response to alectinib compared to the negative control.Cells overexpressing ABCC11 exhibited significantly lower intracellular concentrations of alectinib.In the xenograft model, tumors derived from cancer cells transfected with the ABCC11 expression vector exhibited a higher growth rate following alectinib treatment.
Meng et al. [75]	ABCB1	LUAD, LUSC, Large-Cell Carcinoma (LCC)	Drug response (MTS assay), Gene expression (real time-PCR)	ABCB1 gene expression is positively correlated with IC50 values for paclitaxel.
Xiao et al. [54]	ABCC7	LUAD	Cell Proliferation (live-cell imaging), Gene expression (real time-PCR)	ABCC7 potentiator significantly inhibited cancer cell proliferation in a dose-depend manner.Growth rates of ABCC7 knockdown cells were increased.
Galetti et al. [78]	ABCG2	LUAD, LUSC	Gene expression (western blot), Gene expression (flow cytometry), Intracellular drug conc. (liquid scintillation counting)	ABCG2 knockdown increased intracellular gefitinib levels.ABCG2 overexpression reduced gefitinib accumulation.
Yabuki et al. [76]	ABCB1	LCC	Drug response (CCK-8 assay), Gene expression (real time-PCR)	ABCB1 expression in paclitaxel resistance cells increased significantly.

Table 3. Continued

Han et al. [77]	ABCB1, ABCC1	LUAD, LUSC, Other	Gene expression (real time-PCR)	In chemoresistant blood samples, ABCB1 mRNA levels exhibited approximately twofold to tenfold increases in purified CD56+ cells.For ABCC1 mRNA, chemoresistant blood samples demonstrated approximately onefold to threefold changes. In contrast, chemo-naive blood samples exhibited minimal changes in ABCB1 and ABCC1 mRNA levels.
Chen et al. [85]	ABCC2	LUAD	Drug response (CCK-8 assay), Gene expression (real time-PCR), Gene expression (western blot), Xenograft models (mice)	The expression of ABCC2 had increased significantly in drug-resistant cell lines.The resistance to cisplatin in cells decreased with lower ABCC2 gene expression.The tumour size in xenograft model of the ABCC2 KD group was markedly smaller than that of the other groups.
Oguri et al. [19]	ABCC5	LUAD, LUSC, Large-Cell Carcinoma (LCC)	Drug response (MTS assay), Gene expression (real time-PCR)	A clear association exists between ABCC5 gene expression and sensitivity to gemcitabine.ABCC5 knockdown cells exhibited significantly increased cytotoxicity in response to gemcitabine.
Overbeck et al. [38]	ABCA3	LUADSCLC	Drug response (MTT assay),	ABCA3 KD significantly increased the cytostatic efficacy of cisplatin and paclitaxel. ABCA3 suppression appears to increase susceptibility to vinorelbine.
Uemura et al. [28]	ABCC11	SCLC	Drug response (MTS assay), Gene expression (real time-PCR), Intracellular drug conc. (FPIA)	The gene expression of ABCC11 was increased in drug resistant cell lines.Intracellular methotrexate accumulation was lower in the resistant cells.The methotrexate was more cytotoxic towards ABCC11 KD cells.
Omori et al. [12]	ABCB1, ABCG2	SCLC	Drug response (MTS assay), Gene expression (western blot), Xenograft models (mice)	All etoposide resistant cells showed high ABCB1 expression, and all SN-38 resistant cells showed high ABCG2 expression.ABCB1 KD cells displayed increased sensitivity to etoposide relative to siRNA controls. ABCG2 KD cells displayed a recovery of sensitivity to SN-38.
Boonstra et al. [31]	ABCA2	SCLC	Drug response (MTA assay), Gene expression (real time-PCR), Intracellular drug conc. (FACS)	ABCA2 expression is higher in mitoxantrone resistant cells.Mitoxantrone resistant cells required 1.5- and 2.0-fold higher drug concentrations to achieve IC70 and IC90, respectively.The mitoxantrone accumulation was reduced in mitoxantrone resistant cells.When estramustine was added during incubation with mitoxantrone, mitoxantrone accumulation increased in resistant cells.
Takakuwa et al. [40]	ABCB1	SCLC	Drug response (MTS assay), Gene expression (real time-PCR), Intracellular drug conc. (HPLC)	ABCB1 expression was increased approximately 4, 500-fold in resistant cells.The cytotoxicity to amrubicin in ABCB1 KD cells was increased compared with that in resistant cells.Accumulation of amrubicin in resistant cells was clearly lower.

Table 3 shows non-clinical evidence of ABC transporter related drug resistance in lung cancer. This table summarizes experimental studies using lung cancer cell lines, patient-derived primary cells, or animal xenograft models to evaluate the association between ABC transporter expression and drug sensitivity, cancer cell proliferation, and migration/invasion. For each study, the ABC gene tested, model type, cancer type, drugs tested, assays used to quantify the response, and the main findings are listed.

As a complement to clinical studies, we also included in vitro and animal experiments on the level of expression of ABC genes and their association to clinical drug resistance, cell proliferation, and invasion and metastasis. The ABC genes included were ABCA2, ABCA3, ABCB1, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC7, ABCC11, and ABCG2. Among these, ABCA3, ABCB1, ABCC11, and ABCG2 genes were involved in multiple publications. Unlike clinical studies, the results of non-clinical studies were relatively consistent, which may be due to easier control in in vitro experiments. Notebly, the findings from in vitro experiments may differ from trends observed in clinical results; several ABC genes will be discussed in detail below.

ABCA3 exhibits different functional effects in different experimental settings: Overbeck's in vitro experiments in 2013 supported their result in their clinical findings that ABCA3 silencing increased susceptibility to chemotherapy drugs cisplatin, paclitaxel, and vinorelbine [35]. However, Song et al. observed that ABCA3 knockdown enhanced the proliferation, migration, and invasion of A549 LUAD cells, indicating a potential tumor-suppressive role [36].

Multiple in vitro studies consistently demonstrate an association between ABCB1 level and the Multidrug Resistance (MDR) in lung cancer cells, particularly in response to paclitaxel, etoposide, and amrubicin [12, 38, 74-76]. In cancer cell lines that acquired resistance to paclitaxel, the expression of the ABCB1 gene is significantly increased, along with a decreased sensitivity to paclitaxel [74, 75]. Meanwhile, a two to ten-fold increase in expression levels was also demostrated in CD56+ cells extracted from blood samples of NSCLC patients with drug resistance [76]. In SCLC, increased ABCB1 expression was observed across a broader range of etoposide-resistant cell lines, and this was confirmed by increased sensitivity after ABCB1 knockdown using siRNA [12]. Similar results were obtained in amrubicin-resistant PC-6 cell lines, and an increase in intracellular amrubicin concentration was observed after treatment with the ABCB1 transporter inhibitor verapamil [38].

ABCC11 has also been shown to have a relationship with cancer resistance to various drugs. Overexpression of ABCC11 contributed to chemotherapy resistance to alectinib in NSCLC models, and increased alectinib sensitivity was observed in different cell lines after ABCC11 knockdown [57]. In xenograft models, mice transfected with the H2228 LUAD cell line with upregulated ABCC11 expression showed a significantly increased tumor growth rate [57]. ABCC11 knockdown also increased methotrexate cytotoxicity and intracellular methotrexate accumulation in SCLC models [58].

In vitro studies of ABCG2 generally support its association with poorer clinical outcomes. In NSCLC cell lines, ABCG2 knockdown increased intracellular gefitinib accumulation [77]. In SCLC, cell lines resistant to SN-38 exhibited high ABCG2 expression, and resistance was reversed after knockdown of ABCG2 with siRNA [12].

3.4. Tumor-intrinsic prognostic associations in untreated cohorts (TCGA/cBioportal)

Table 4. Prognostic association of ABC transporter expression in untreated TCGA lung cancer cohorts

Gene	LUAD (OS association)	*p* value	LUSC (OS association)	*p* value
ABCA2	Not significant	-	Low expression → better OS	0.041
ABCA3	High expression → better OS	0.0024	Low expression → better OS	0.0040
ABCB1	Not significant	-	Not significant	-
ABCC1	Not significant	-	Not significant	-
ABCC2	Not significant	-	Not significant	-
ABCC3	Not significant	-	Not significant	-
ABCC4	Not significant	-	Not significant	-
ABCC5	Not significant	-	Not significant	-
ABCC7	High expression → better OS	0.0033	Not significant	-
ABCC11	Low expression → better OS	0.019	Not significant	-
ABCG2	Not significant	-	Not significant	-
ABCG4	Not significant	-	Not significant	-

Table 4 shows prognostic association of ABC transporter expression in untreated TCGA lung cancer cohorts. This table summarizes experimental studies using lung cancer cell lines, patient-derived primary cells, or animal xenograft models to evaluate the association between ABC transporter expression and drug sensitivity, cancer cell proliferation, and migration/invasion. For each study, the ABC gene tested, model type, cancer type, drugs tested, assays used to quantify the response, and the main findings are listed.

To assess baseline prognostic associations independent of chemotherapy exposure, overall survival analyses were performed using lung cancer datasets from The Cancer Genome Atlas (TCGA) via cBioPortal--a cancer genomics platform that integrates clinical data and multi-dimensional cancer genomic datasets—for LUAD and LUSC [78]. TCGA is a cancer genomics project that encompasses tissue samples and related data, including genomic, transcriptomic, proteomic, and clinical data, for 33 types of cancer [79]. As TCGA samples were largely obtained prior to systemic treatment, these analyses largely reflect tumour-intrinsic biology rather than treatment response.

Most ABC transporters showed no significant association with OS, suggesting that the correlation between ABC genes and clinical outcomes may be more dependent on drug resistance during treatment. Exceptions with significant associations included ABCA2, ABCA3, ABCC7, and ABCC11. For ABCA2, only in LUSC was lower ABCA2 expression significantly related with improved OS ($p = 0.041$), while no significant OS association was detected in LUAD.

The clinical outcome of ABCA3 was strongly context-dependent histologically, with opposite association directions in LUAD and LUSC. In LUAD, higher ABCA3 expression was related with better OS ($p = 0.002435$), while in LUSC, lower ABCA3 expression was related with better OS ($p = 0.003992$).

In contrast, ABCC7 showed a significant association only in LUAD, where higher ABCC7 expression was related with improved OS ($p = 0.003332$), with no significant association in LUSC. This aligns with long-standing research on ABCC7, including its roles in suppressing NFκB activity and controlling epithelial-to-mesenchymal transition [52].

Finally, ABCC11 showed an unfavorable prognostic pattern in LUAD, with lower ABCC11 expression has an association with better OS ($p = 0.019$), while no significant association was detected in LUSC. This may stem from ABCC11's pro-cancerous roles in lymph node metastasis and venous invasion [59].

Overall, the association between ABC transporter level and OS in the untreated cohort from the database differed across different cancer subtypes (LUAD/LUSC). Furthermore, the discrepancies between the untreated cohort and clinical and in vitro experiments suggest that different ABC genes contribute differently to patient prognosis; some ABC transporters only affect the MDR phenotype by regulating drug efflux, while others possess intrinsic biological mechanisms.

4. Discussion

Multidrug resistance in lung cancer represents a significant barrier to patient survival, largely attributable to drug efflux phenotype mediated by ABC transporters [10]. However, the relationship between ABC transporters and clinical outcomes remains controversial. This systematic review integrates clinical and pre-clinical studies on lung cancer across the past 25 years, combined with analysis of untreated cohorts from TCGA/cBioPortal, aiming to establish an summary of the impact of ABC transporters on lung cancer prognosis and offer insights into current research.

First, clinical studies of chemotherapy-treated lung cancer patients show substantial heterogeneity in the association between ABC transporter expression and treatment response, particularly for ABCB1, ABCC1, and ABCG2. In multiple studies, they are associated with poorer treatment response or shorter survival, but there is significant heterogeneity across studies. The sources of this heterogeneity are diverse: different chemotherapy regimens are used in different studies, and the specificity of ABC transporters to these drugs also varies [25]. ABC transporters exhibit substrate specificity, and when regimens include agents that are not primary substrates of a given transporter, associations with clinical response may be attenuated or obscured. Furthermore, relatively few studies have systematically evaluated ABC expression across standardized treatment regimens, limiting cross-study comparability. In addition, the heterogeneity of research results may also stem from the varying influence that different ABC transporters exert on each stages of cancer progression [11, 80]. This is consistent with a clinical study covering breast cancer, colorectal cancer, and pancreatic cancer, which found that the upregulation or downregulation of different ABC transporters was associated with tissue grading or clinical stage [81]. Besides, the cancer subtypes (e.g., LUAD versus LUSC), adjuvant therapy, and tissue extraction time points of the patients involved in different studies can also affect clinical outcomes.

In contrast, in vitro and in vivo experimental studies demonstrate greater consistency in linking ABC transporter expression to drug resistance phenotypes. These models typically evaluate defined chemotherapeutic agents under controlled conditions, allowing clearer identification of transporter–drug relationships. For example, experimental studies consistently associate ABCB1 expression with resisting phenotype to chemotherapy drugs such as etoposide and paclitaxel [12, 38, 74-76]. In clinical settings, however, treatment regimens are more heterogeneous and often combine multiple drugs, which may dilute or confound substrate-specific effects [11, 23, 25, 65]. Discrepancies between experimental and clinical findings therefore likely reflect biological and therapeutic complexity rather than contradiction of the underlying MDR mechanism. Moreover, clinical outcomes are influenced by tumour microenvironment, host factors, and treatment variability, all of which are difficult to replicate in controlled experimental systems. A 2013 in vitro study by Zhao et al. has shown that increased ABCC3 mRNA expression occurred in all primary cell lines obtained from NSCLC patients that were resistant to paclitaxel, docetaxel, gemcitabine, vinorelbine, and cisplatin [82]. However, a 2004 clinical study by Yoh et al., which included chemotherapy regimens including the five drugs above, no linkage between ABCC3 expression and patient survival was found [25].

Analysis of untreated TCGA cohorts supports the interpretation that the clinical impact of most ABC transporters on lung cancer outcomes is primarily treatment-dependent rather than intrinsic. In the absence of drug treatment or chemotherapy, expression levels of four ABC transporters—ABCA2, ABCA3, ABCC7, and ABCC11—have a significant association with overall survival time. In mice with transgenic adenocarcinoma of the prostate, the study has shown that ABCA2 may promote metastasis/migration of cancer cells through sphingolipid metabolism [29]. For ABCA3, one study has shown that ABCA3 regulates cancer proliferation, migration, and invasion by downregulating the expression levels of E-cadherin, N-cadherin, and retinoic acid, which are important in the Epithelial-Mesenchymal transition process [36]. For ABCC7, multiple studies reported its anti-cancer role, such as inhibiting cancer proliferation and regulating invasion and the EMT process, as well as its anti-inflammatory role, which was confirmed in clinical outcomes and in vitro experiments [52, 53, 83]. Lastly, a study on colon cancer patients reported an association between ABCC11 overexpression and cancer phenotypes involving lymph node metastasis and venous invasion [59].

5. Conclusion

Taken together, the evidence suggests that ABC transporters primarily function as predictive markers of chemotherapy response in lung cancer, while a limited subset may also contribute to intrinsic tumor biology and overall survival. The substantial heterogeneity across clinical studies underscores the need for more rigorous and standardized analytical frameworks. Future investigations should incorporate standardized analytical procedures, including stratifying patient populations by treatment regimen, cancer subtype, cancer stage, and clinical endpoints. Integrating pre-clinical experimental evidence with well-controlled clinical cohorts will be essential to determine whether specific ABC transporters can be reliably developed as predictive biomarkers or therapeutic targets in lung cancer.

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