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Association between incidence of hypomagnesemia and better prognosis of NSCLC: A case on the immortal time bias

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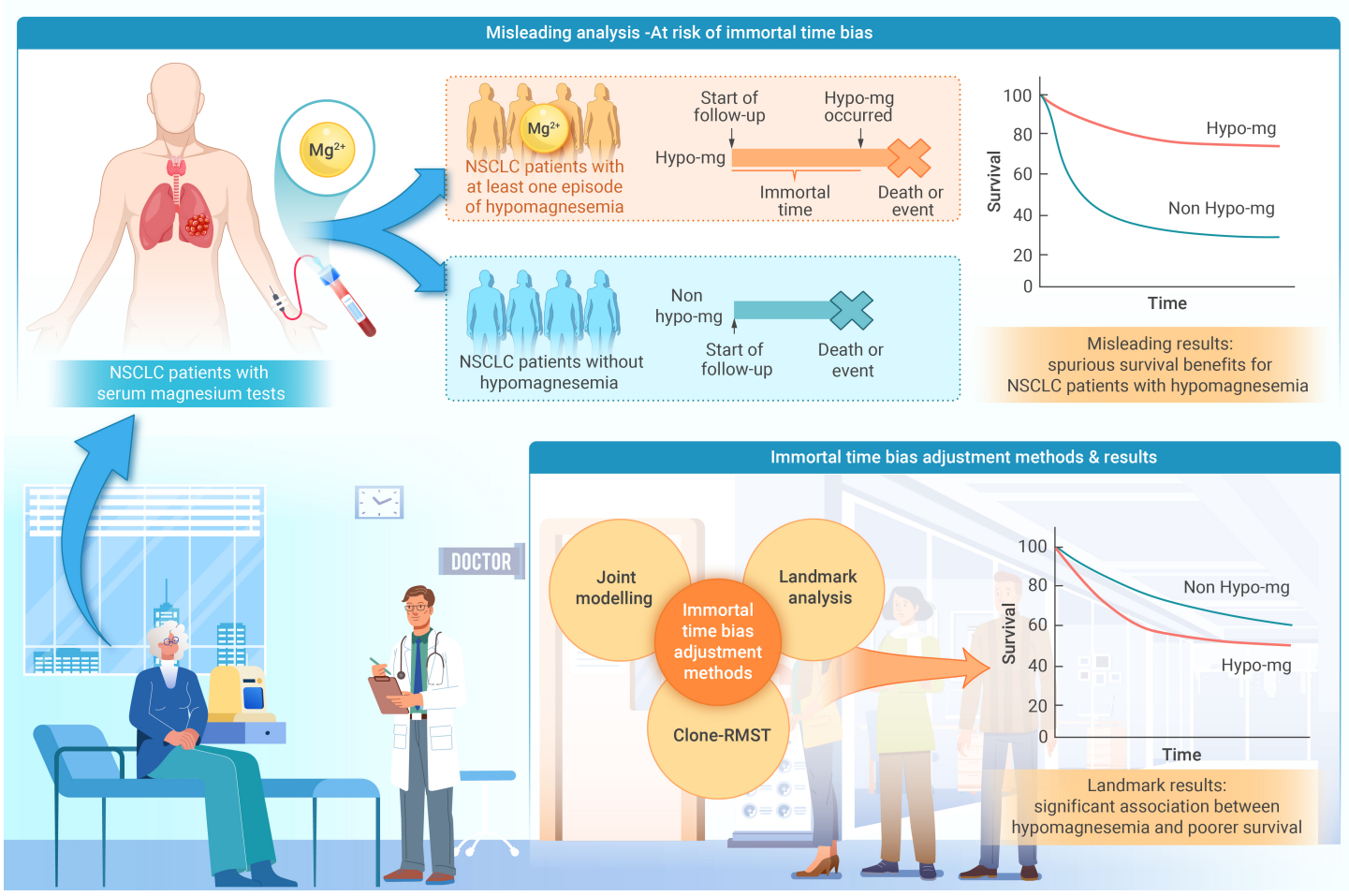
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Immortal time bias (ITB) was pervasive and detrimental in clinical follow-up studies.
- Due to ITB risk, spurious negative associations between hypomagnesemia and cancer prognosis were reported.
- Greater attention should be given to ITB in study design and analysis, with emphasis on time zero.
- To address ITB, appropriate approaches should align with study population, research objective, and estimand.
- The development and adoption of guidelines for controlling ITB are strongly advocated.

REPORT

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Background: Previous studies predominantly reported that the occurrence of hypomagnesemia was associated with improved cancer prognoses. However, utilizing publicly available data, we demonstrated the presence of bias in this association, attributable to the failure to account for immortal time bias (ITB) when grouping patients based on post-therapeutic characteristics/variates. Methods: This research included 4,172 individuals from four clinical trials of Atezolizumab (NCT02366143, NCT02367794, NCT02367781, NCT02008227) in non-small cell lung cancer (NSCLC). Joint modelling, landmark, and clone-RMST (restricted mean survival time) methods were performed to remove ITB. Previous studies about hypomagnesemia and prognosis in cancers were pooled. Results: Under the risk of ITB, spurious benefits in progression-free survival (PFS) and overall survival (OS) were observed in patients with at least one episode of hypomagnesemia, based on our research and previous studies. When controlling for ITB, the initially observed false beneficial effect disappeared, revealing a significant association between hypomagnesemia and worse OS [HR: 1.01 (1.00, 1.02), *P*=0.0330] in joint modelling. A similar trend was observed in PFS [HR: 1.01 (1.00, 1.02), *P*=0.0564]. Consistent results were obtained from landmark and clone-RMST analysis. The estimands and application scenarios of the three methods were compared and discussed. Conclusions: Three methods were utilized and recommended to control ITB. Time zero definition should be emphasized to avoid ITB with advocacy of guidelines. In NSCLC, serum magnesium levels could serve as a potential prognostic biomarker in first-line therapy, but not in non-first-line therapy.

INTRODUCTION

Lung cancer was the most prevalent tumor and the leading cause of death worldwide and in China in 2,022.[1-3] Targeted therapy and immunotherapy have enhanced prognosis of non-small cell lung cancer (NSCLC), extending both progression-free survival (PFS) and overall survival (OS). Prognostic prediction and identification of prognosis factors have been prominent in cancer research.[4-7] In the realm of NSCLC, it has been a common practice to rely on specific events for predicting prognosis. For instance, the manifestation of hand-foot syndrome typically signified the effectiveness of tyrosine kinase inhibitors (TKIs), while immune-related adverse events commonly served as predictors for survival benefits of PD-(L)1.[8,9] Furthermore, the occurrence of hypokalemia was associated with a more favorable response to anti-EGFR targeted therapy.[10]

Previously, the correlation between dietary intake of electrolytes and lung cancer incidence were reported.[11] Mechanistic studies have reported that electrolytes, including magnesium, sodium, and potassium, act as components of microenvironment, influencing the regulation of immune response.[12-14] Magnesium (Mg^{2+}) is an essential ion playing an instrumental role in cell proliferation, differentiation, migration, and apoptosis.[15] However, conflicting findings have emerged in multiple studies regarding the prognostic significance of hypomagnesemia in cancer patients. Some studies suggested that hypomagnesemia predicted better survival, while others did not.[16,17] Crucially, it is imperative to note that these results may be susceptible to immortal time bias (ITB).

The presence of ITB was commonly attributed to flaws in study design or data analysis; regrettably, it was frequently disregarded by researchers. Immortal time refers to a follow-up period during which no event (study outcome, e.g. death or disease progression) can occur due to the definition of exposure.[18] Bias arises when individuals are divided into comparison groups based on a potential factor that was unknown at study entry (baseline) but later identified (a time-delayed exposure) during the follow-up period (in the future).[19] Patients are grouped based on this post-baseline exposure, with the assurance that those in the exposure group will not experience the study outcome before the occurrence of exposure. If patients experienced the study outcome before the occurrence of exposure, they would be categorized into non-exposure group, or control group. Patients in the exposure group are susceptible to immortal time, while patients in the control group are not. This susceptibility leads to an exaggerated or false inverse association being attributed to exposure, ultimately resulting in a spurious advantage for exposure. ITB commonly occurs in observational studies and post-hoc analyses, where clinical trials are considered as cohorts.

Therefore, we conducted this post-hoc analysis to demonstrate the influence of ITB on the association of hypomagnesemia and prognosis. We emphasized the importance of carefully defining time-zero to avoid ITB in clinical follow-up studies. Our initial objective was to examine the potential impact of hypomagnesemia on prognosis with presence and absence of ITB using patient-level data from clinical trials. Subsequently, we explored various approaches to mitigate ITB and discussed their corresponding estimand and analysis. Finally, we collected and pooled previous studies on hypomagnesemia and survival across diverse tumor types, categorizing them based on whether ITB was addressed, to summarize its impact and the valid association.

MATERIALS AND METHODS

Data Source

Individual-level data were from four phase III multi-center randomized controlled trials involving 4,172 advanced NSCLC patients, who received different line therapies with or without Atezolizumab (IMpower150, NCT02366143; IMpower131, NCT02367794; IMpower130, NCT02367781; OAK, NCT02008227). The data profile and summaries are presented in Figure 1 and Table S1, respectively. Detailed descriptions were published elsewhere.[20-23]

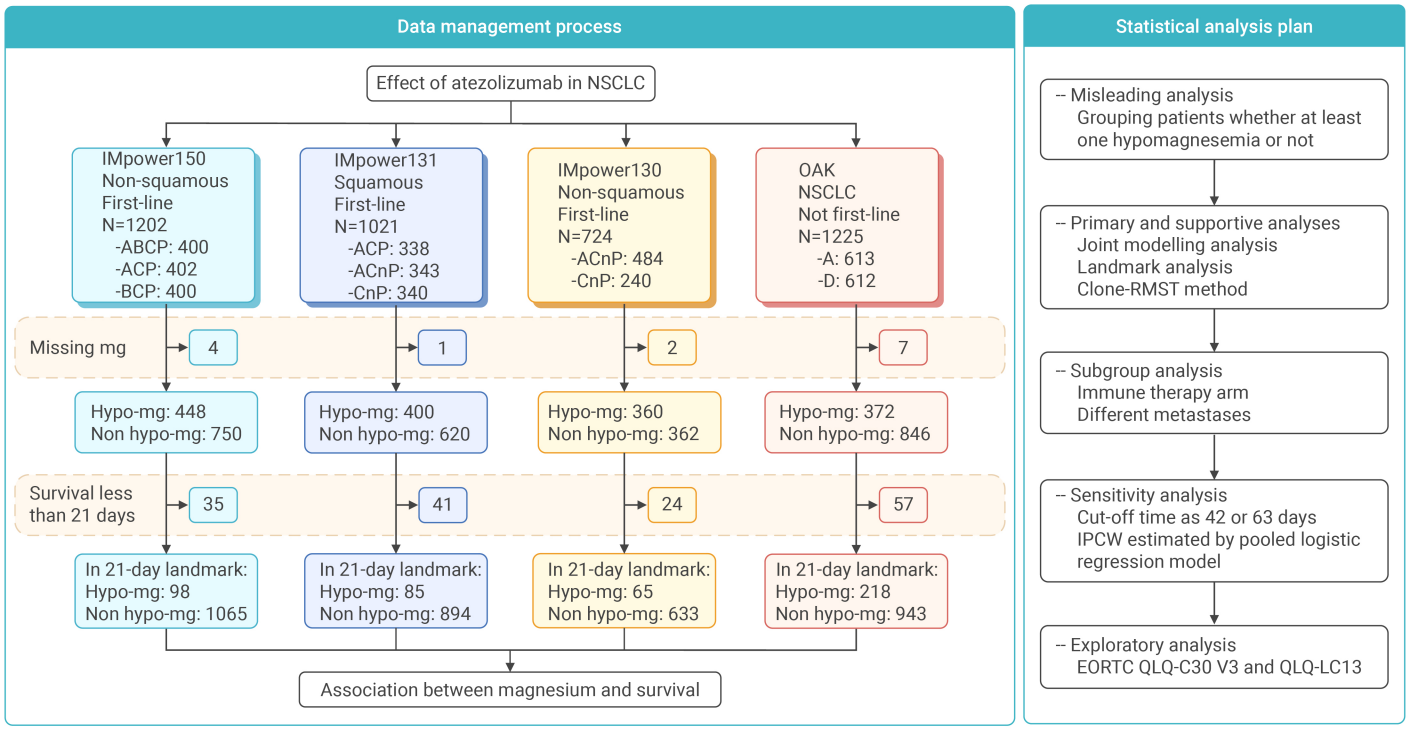

Figure 1. Data profile and analysis steps Hypo-mg: hypomagnesemia; mg: magnesium; NSCLC: non-small cell lung cancer. A: atezolizumab; B: bevacizumab; C: carboplatin; P: paclitaxel; nP: nab-paclitaxel; D: Docetaxel. RMST: restricted mean survival time, IPCW: inverse probability of censoring weight, OS: overall survival, PFS: progression-free survival. EORTC: European Organization for Research and Treatment of Cancer. QLQ-C30 V3: Quality of Life Questionnaire - Core 30 version 3. QLQ-LC13: Quality of Life Questionnaire - Lung Cancer 13.

Outcome

OS and PFS were assessed as co-primary endpoints in the three trials with first-line therapy (IMpower150, IMpower131, and IMpower130), and as primary and secondary endpoints in OAK with non-first-line treatment, respectively. To account for all serum magnesium measurements, the start date for OS/PFS was defined as the initial laboratory record.

Quality-of-life questionnaires

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30) version 3, alongside the supplemental lung cancer module, QLQ-LC13, were utilized to assess patients' quality of life. The QLQ-C30 comprises five multi-item scales evaluating functioning (physical, emotional, role, cognitive, and social), three multi-item scales measuring symptoms (fatigue, nausea/vomiting, pain), six single-item symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a comprehensive global health status/quality of life scale.[24] Additionally, the QLQ-LC13 module includes a multi-item scale specific to dyspnea and several single-item scales addressing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis.[25] Each item is rated on a scale ranging from 1 to 4, or 1 to 7 for the global health status, and these ratings are then converted linearly to a scale score between 0 and 100. Higher scores indicate a higher level of response, which can signify increased symptom severity, better functional status, or enhanced health-related quality of life.

Blood Magnesium Level

Blood magnesium level (mmol/L) was measured in the serum chemistry test at screening and every 21 days (3 weeks) during all anti-cancer treatment cycles. The reported laboratory results included numerical values, units, reference ranges, and clinical significance. Hypomagnesemia or non-hypomagnesemia was defined by whether the blood magnesium level was below the lower limit of the reference range. For the analysis involving continuous serum magnesium, magnesium values underwent a natural base logarithmic transformation, scaling, and subsequent standardization based on different reference ranges.

Covariates in Models

To account for the potential confounding and population heterogeneity, covariates adjusted in our analysis include treatment arms, age, sex, race, Eastern Cooperative Oncology Group (ECOG) performance status, tobacco use, immune cell score, histology type (non-squamous, squamous) and number of prior therapies based on previously reported post-hoc analyses of clinical trials involving Atezolizumab.[26] Considering the potential effect of serum magnesium on tumor proliferation and metastasis, we additionally controlled the stage at diagnosis and the number of metastatic sites.[27]

Statistical Analysis

To demonstrate the impact of ITB, we initially conducted the 'misleading analysis' that, although commonly used, were susceptible to this bias. Patients were categorized into hypomagnesemia and non-hypomagnesemia groups according to whether at least one episode of hypomagnesemia happened before the outcome events (death or disease progression). This grouping introduced ITB, as patients in the hypomagnesemia group were considered "immortal" until hypomagnesemia occurred - a condition not applicable to the non-hypomagnesemia group. The immortal time in the hypomagnesemia group resulted in a misleading reduction in event risk and overestimation of survival time for this group. We used Kaplan-Meier curves and log-rank tests for comparisons of PFS and OS between hypomagnesemia and non-hypomagnesemia groups in the misleading analyses.

To control ITB, we employed three analytic strategies (Figure 1). Firstly, as the primary analysis, we considered serum magnesium as a time-dependent exposure and performed joint modelling to investigate the average association between serum magnesium and survival throughout the entire follow-up.[28] A meta-analysis would be performed to pool results and explore heterogeneity among four trials. Joint modelling was a method that could simultaneously analyze longitudinal measurements and survival data with two linked sub-models. The generalized linear mixed effects sub-model specified the time course of time-dependent measurements. Cox proportional hazards model was utilized to estimate hazard ratios (HRs) for survival data. Joint modelling was performed using the R package "JMbayes2", employing the Bayesian approach and the Markov Chain Monte Carlo algorithms (details

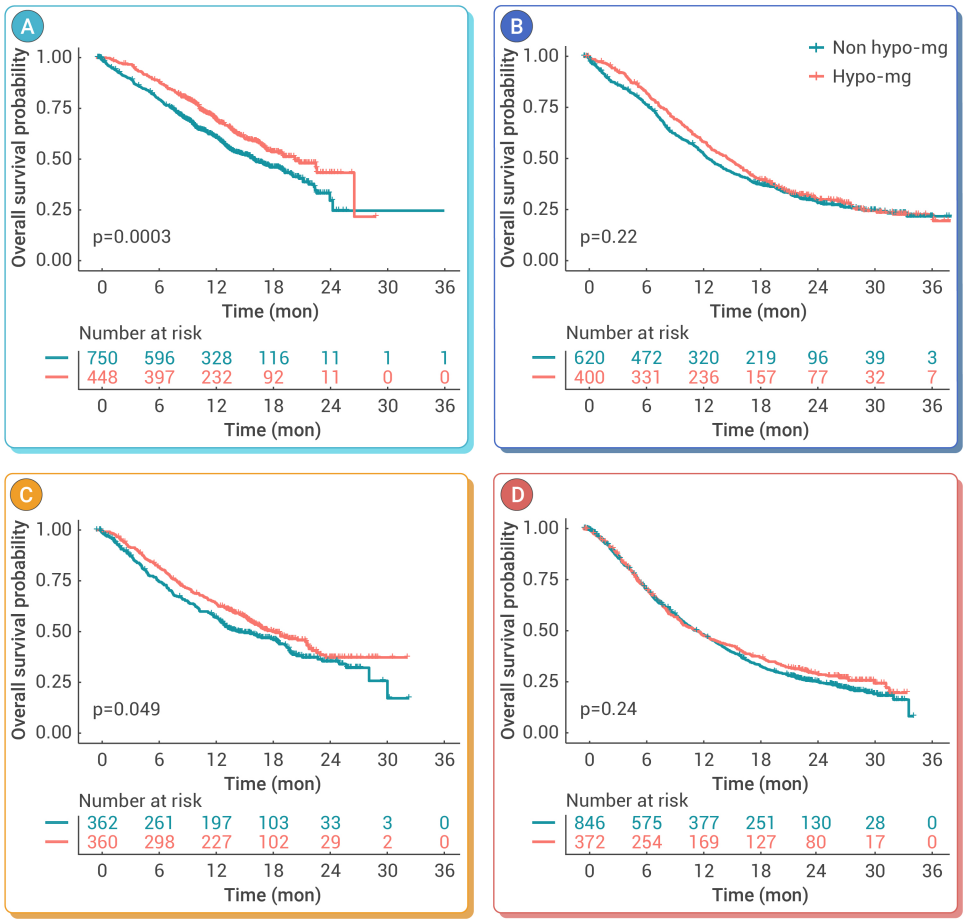

Figure 2. Under the risk of immortal time bias, Kaplan-Meier curves for overall survival (OS) among patients whether hypomagnesemia occurred in any laboratory test Hypo-mg: hypomagnesemia. (A): IMpower150, (B): IMpower131, (C): IMpower130, (D): OAK.

were described in the Supplementary Methods). All the above-mentioned covariates, and baseline serum magnesium, were adjusted. Secondly, as supportive analyses, landmark analysis and clone-RMST method were applied to explore the association of early-onset hypomagnesemia and survival. In landmark analysis, only patients without disease manifestations or those who were alive beyond the cut-off date, which was set as the 21st day after randomization, were included. Patients were divided into hypomagnesemia and non-hypomagnesemia groups based on whether they experienced at least one hypomagnesemia before the cut-off date. Any hypomagnesemia occurring after the cut-off date was ignored.[9] In clone-RMST method, duplicates of every eligible participant were generated at the start of follow-up (the date of initial laboratory record).[29] Two replicates were assigned to either hypomagnesemia group or non-hypomagnesemia group, respectively. Patients in the hypomagnesemia group were artificially censored at the cut-off date (21st day after randomization) if they did not experience hypomagnesemia, while those assigned to the non-hypomagnesemia group were censored when hypomagnesemia developed during the follow-up. In cloning procedure, it should be noted that the artificial censoring produces informative censoring (potential selection bias over time), and the inverse probability of censoring weighting (IPCW) was employed through Cox regression model.[29,30] Furthermore, since the cloning step would violate the proportional hazard assumption, the restricted mean survival time (RMST) method was performed to compare survival between groups.[29] Non-parametric bootstrap with 500 replications was utilized to estimate 95% CIs. In sensitivity analyses, alternative cut-off dates, the 42nd day and 63rd day after randomization, were considered in landmark and clone-RMST method. To confirm the robustness of the clone-RMST method, IPCW analyses were conducted using pooled logistic regression model, incorporating time-varying covariates such as age, ECOG performance status, and continuous serum magnesium levels, as well as the time-invariant covariates mentioned earlier. Subgroup analyses were conducted among patients receiving Atezolizumab therapy to evaluate the consistency of associations across diverse therapeutic contexts. Additionally, we delved into the correlation between serum magnesium levels and prognosis in individuals with distinct metastatic sites, with the objective of elucidating potential heterogeneity in metastatic patterns. This investigation was spurred by intricate results from mechanistic studies, which have indicated a potential link between magnesium and both tumor progression and metastasis, warranting further exploration. Data was authorized by Roche Data Sharing Team and analyzed using R software (version 4.1.1) on the Vivli (https://vivli.org/) platform.

Systematic Review of Previous Studies about Hypomagnesemia and Prognosis

We reviewed published reports about the effect of serum magnesium on the survival of cancer patients from PubMed as of 31st, December 2024. An electronic literature search was conducted using keywords "hypomagnesemia", "hypomagnesaemia", "magnesium" "mg" "magnesium disorder" "magnesium modification", "cancer", "carcinoma", "malignancy", "tumor", "efficacy", "effect", and "prognosis". The search was restricted to papers published in English. Letters and conference abstracts were excluded. Relevant reviews and meta-analyses were also examined to identify eligible studies. The research was included based on the following criteria: patients diagnosed with tumors; studies that reported hazard ratios (HRs) for PFS and/or OS associated with serum magnesium/ hypomagnesemia which occurred during treatment or after the first dose of therapy. Studies on baseline serum magnesium and cancer prognosis were excluded because they were not related to ITB. The following information was abstracted from the included studies: first author, publication year, cancer type, line of treatment, intervention, number of patients, comparison, PFS, OS, and HR. We classified eligible studies into two categories, namely those controlling for immortal time bias and those at the risk of immortal time bias based on whether the potential impact of the bias was properly accounted for in statistical analysis. Due to the substantial heterogeneity, random effect models were applied to pool the HRs within each category, except in cases where there were fewer than three studies.

Exploratory analysis

To explore the association between serum magnesium levels and quality-of-life outcomes, we performed linear mixed-effect model to assess the correlation between serum magnesium levels (including continuous serum magnesium levels, changes from baseline, and the presence of hypomagnesemia) and the quality-of-life questionnaires (including EORTC QLQ-C30 V3 and EORTC QLQ-LC13).

RESULTS

Patients Characteristics

This analysis included participants from IMpower150 (*N*=1,202), IMpower131 (*N*=1,021), IMpower130 (*N*=724), and OAK (*N*=1,225), with a total sample size of 4,158 patients who had the laboratory test of serum magnesium (Figure 1). We observed potential confounding bias presented as an imbalance at the standardized mean difference (SMD) of more than 0.1 among groups (Tables S2-S9).

Table 1. Studies of effect of hypomagnesemia on progression-free survival (PFS) and overall survival (OS) among cancer patients after treatment in PubMed.

Source	Publication Year	Cancer Location	Therapy line	Comparison	Sample size	PFS (months)	HR	OS (months)	HR
Category 1. Only patients survived longer than the observational window of magnesium reduction (Controlling immortal time bias)									
Vickers et al.	2012	Colorectal	FL	Hypo-mg vs non-hypo-mg	572	NA	1.10 (0.78-1.57)	3.7 vs 8.0	1.60 (1.10-2.31)
				Magnesium reduction (≥ vs < 20%)		NA	1.70 (1.10-2.65)	3.8 vs 7.6	2.01 (1.28-3.16)
Category 2. All cancer patients after anti-tumor treatment (Risk of immortal time bias)									
Vincenzi et al.	2008	Colorectal	NFL	Magnesium reduction (> vs ≤ 20%)	68	6.0 vs 3.6	0.19 (0.10-0.34)	10.7 vs 8.9	NA
Vincenzi et al.	2010	Colorectal	NFL	Magnesium reduction (> vs ≤ 50%)	143	6.3 vs 3.6	0.14 (0.11-0.28)	11.0 vs 8.1	NA
Fujii et al.	2016	Colorectal	NFL	Hypo-mg vs non-hypo-mg	43	9.0 vs 4.3	0.67 (0.36-1.25)	NA	NA
Price et al. [a]	2016	Colorectal	NFL	Hypo-mg vs non-hypo-mg	496	6.7 vs 3.0	0.46 (0.38-0.56)	13.6 vs 8.7	0.63 (0.51-0.78)
			NFL	Hypo-mg vs non-hypo-mg	503	6.6 vs 3.2	0.54 (0.43-0.69)	12.6 vs 9.3	0.71 (0.56-0.90)
Kimura et al. [a]	2020	Colorectal	NFL	Hypo-mg vs non-hypo-mg	37	NA	NA	19.1 vs 23.6	NA
			NFL	Hypo-mg vs non-hypo-mg	31	NA	NA	18.9 vs 17.3	NA
Liu et al.	2019	Ovarian	NFL	Frequency of hypo-mg	229	NA	NA	NA	1.05 (1.02-1.09)
Liu et al.	2020	HNC	NFL	Frequency of hypo-mg	439	NA	NA	NA	1.13 (1.01-1.26)
Xu et al.	2024	NSCLC	NA	≥ 0.73 mmol/L vs < 0.73 mmol/L	91	11.93 vs 6.70	NA	28.78 vs 11.37	NA
Overall (Category 2)	NA	NA	NA	NA	1,253/1,667	NA	0.34 (0.19-0.62)	NA	0.87 (0.66-1.15)

[a] These studies performed analysis of magnesium effect in two different treatment arms.

Abbreviations: PFS: progression-free survival. OS: overall survival. Hypo-mg: hypomagnesaemia. HR: Hazard ratio. NA: Not applicable. FL: First line. NFL: Non first line. HNC: Head and neck cancer. NSCLC: non-small cell lung cancer.

Impact of the Immortal Time Bias

The spurious protective effect of hypomagnesemia on OS was observed in IMpower150, and 130, and similar results could be observed in IMpower131 and OAK without significance (Figure 2). Meta-analysis of previous studies that were at the risk of ITB showed a similar trend, with HR as 0.87 (95% CIs: 0.66-1.15, *P*=0.3204) (Table 1). When PFS was evaluated as the outcome, both IMpower150, IMpower130, and OAK demonstrated a spurious negative association between hypomagnesemia and prognosis (Figure S1). Consistent results were observed in the meta-analysis of previous studies conducted across different types of cancers (HR: 0.34, 95% CIs: 0.19-0.62, *P*=0.0004) (Table 1).[17,31-37] However, upon controlling for ITB, inconsistent and even contradictory results were observed. Significantly longer OS were claimed in non-hypomagnesemia group in IMpower130, as well as PFS in IMpower131 (Figures 3 & S2). Of the previous studies included, only one properly accounted for ITB using landmark analysis, uncovering the positive association between hypomagnesemia and prognosis [HR for PFS: 1.10 (0.78-1.57); HR for OS: 1.60 (1.10-2.31)] in colorectal cancer.[16] When comparing whether magnesium reduction was greater than 20% or not, significant associations were identified with both PFS and OS [HR for PFS: 1.70 (1.10-2.65); HR for OS: 2.01 (1.28-3.16)] (Table 1).

Association between Hypomagnesemia and Prognosis

We observed a significant association between the exposure of hypomagnesemia and worse OS, with the HR as 1.01 (1.00-1.02, *P*=0.0330). Heterogeneity among these four trials was claimed (I square: 0.5544, P for heterogeneity: 0.0809) (Figure 4). Positive association could be observed in IMpower150 and IMpower130 with HRs as 1.03 (1.00-1.06, *P*=0.02) and 1.04 (1.01-1.08, *P*=0.0044) in the joint modelling analysis (Table 2). Serum magnesium levels and the change from baseline were found to increase with improved OS [HR: 0.80 (0.71, 0.91, *P*=0.0005); HR: 0.80 (0.70, 0.91), P=0.0007] (Figure 4). Similarly, heterogeneity was observed, and significant association was claimed in all trials except OAK (Table 2). Result for the association between early-onset hypomagnesemia and worse OS was claimed in IMpower130 in landmark analysis [Median OS, hypomagnesemia vs. non hypomagnesemia: 8.54 (95% CI: 7.23-15.60) vs. 18.92 (95% CI: 16.76-20.40) months, *P*<0.0001], and IMpower131 [shorter restricted mean survival time (RMST) in hypomagnesemia group: -3.01 (95%CI: -5.72, -0.30) months] and 130 [-5.73, (-8.10, -3.36) months] in clone-RMST (Figures 3 & S3).

A similar association between the exposure of hypomagnesemia and PFS was observed without significance (HR: 1.01, (1.00-1.02, *P*=0.0564) but with heterogeneity (I square: 0.7469, P for heterogeneity: 0.0079) (Figure 4). However, worse PFS was claimed for the hypomagnesemia in IMpower150 and IMpower131 with HRs as 1.04 (1.02-1.07, *P*<0.0001) and 1.00 (1.00-1.01, *P*=0.0389) (Table 2). Consistent with OS findings, serum magnesium levels and the change from baseline were negatively associated with PFS in pooled results [HR: 0.78 (0.70, 0.86, *P*<0.0001); HR: 0.78 (0.70, 0.88), P<0.0001] and all trials except OAK (Figure 4, Table 2). For early-onset hypomagnesemia, shorter PFS was observed in IMpower131 in both landmark analysis [5.68 (4.90-6.54) vs. 6.41 (6.01-7.06) month, *P*=0.009] and clone-RMST [-2.76 (-4.77, -0.75) months] (Figures S2-S3).

Association between serum magnesium levels and quality-of-life questionnaires

We observed a robust association between serum magnesium levels (including continuous standardized levels, changes from baseline, and the presence of hypomagnesemia) and quality-of-life assessments using the EORTC QLQ-C30 V3 and EORTC QLQ-LC13 questionnaires. Specifically, all

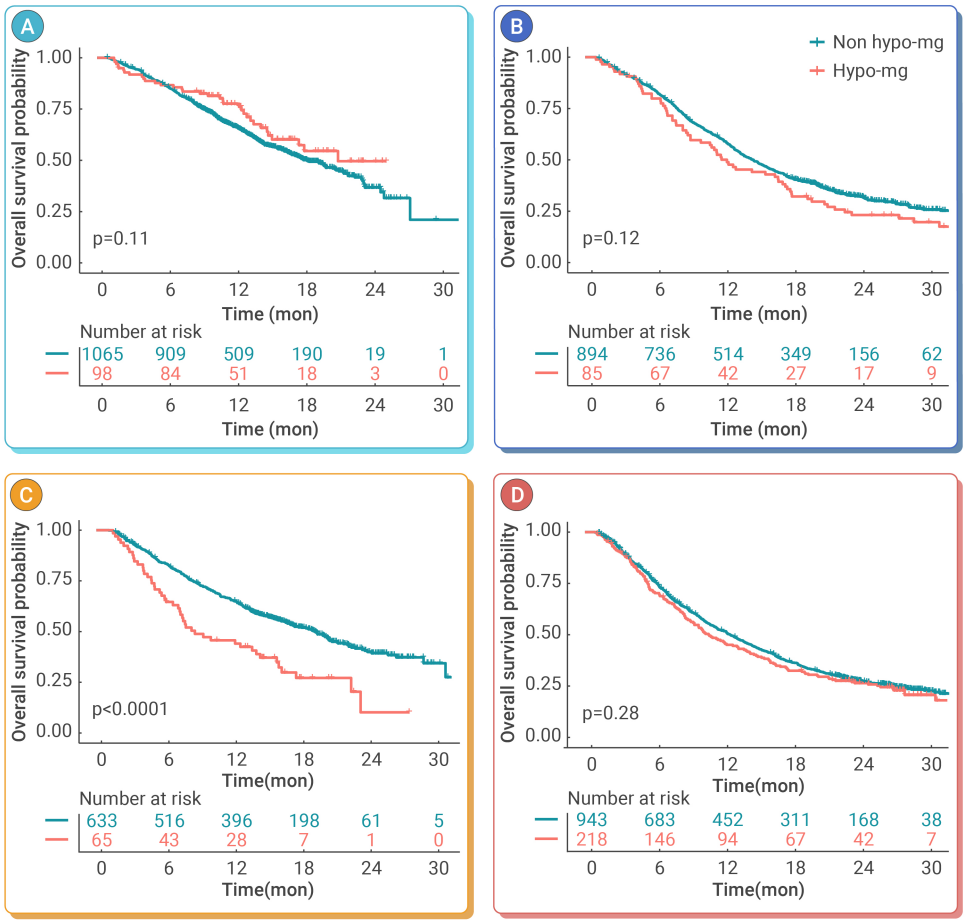

Figure 3. Kaplan-Meier curves with 21-day landmark analysis for overall survival (OS) in patients with or without hypomagnesemia Hypo-mg: hypomagnesemia. (A): IMpower150, (B): IMpower131, (C): IMpower130, (D): OAK.

15 items in the QLQ-C30 and 10 items in the QLQ-LC13 were found to be associated with at least one aspect of serum magnesium levels. Notably, in the QLQ-C30, the diarrhea symptom scale, fatigue symptom scale, physical symptom scale, global health status scale, role functional scale, and social functional scale exhibited correlations with serum magnesium levels across all four trials. Similar findings were observed for the alopecia and dyspnea items in the QLQ-LC13 (Tables S11-S14).

Subgroup and sensitivity analyses

In subgroup analyses (Table S10, Figures S4-S6) and sensitivity analyses (Figures S7-S15), similar results were observed. However, in the case of non-first-line therapy in OAK, serum magnesium exhibited no discernible impact on either OS or PFS in most analyses (Table 2, Figure 3, Figures S2-S3).

DISCUSSION

Our findings indicated that the existence of pervasive and detrimental ITB could induce a falsely negative association between hypomagnesemia and prognosis in various cancers. Upon addressing ITB, the spurious negative association was nullified, and instead, a positive association was asserted, irrespective of treatment modalities in the first-line therapy of NSCLC. This finding was consistent with the previous study considering ITB. In contrast, in the non-first-line therapy, the relationship between hypomagnesemia and survival was not observed. Caution should be exercised regarding ITB when categorizing patients based on characteristics identified during the follow-up period.

ITB was first identified in the 1970s, and various methods or strategies were developed to mitigate its impact.[38,39] Three innovative and practical methods, including joint modelling, landmark analysis, and clone-RMST methods, were employed in our study.[28-29,40-41] Joint modelling was a presentative method that utilized a time-dependent definition of exposure, encompassing both categorical and continuous exposure, which is one among a series of strategies that also involve the time-dependent Cox model and person time approach.[42] These methods allowed individuals to contribute to both exposure and non-exposure statuses during the follow-up period and facilitated status transformation. The HRs derived from joint modelling provided a measure of the average effect of exposure over the entire follow-up period, relative to the non-exposure status. However, estimation of precise survival time was infeasible using this method due to non-specific patient subgrouping, which could potentially complicate the interpretation of findings to clinicians. The main advantage of joint modelling over misleading analysis was the correct consideration of marker value with measurement error at the cost of intensive computation. Landmark analysis was the most pragmatic approach that categorized patients according to the exposure status within a pre-specified interval, excluding participants who were dead or censored during the window period. This exclusion ensures the balance of immortal time between the exposure and non-exposure groups, thus avoiding the exaggerated or spurious benefits of the exposure. The choice of the assessment interval was largely subjective, and appropriate consideration from clinical expertise was vital. Different intervals were crucial for robustness and reliability of the results in sensitivity analyses. The exposure definition overlooked the exposed status after the assessment interval, which could introduce additional misclassification bias from multiple late-time exposures. The estimated HRs and survival curves examined the relationship between early-onset exposure and outcome in patients who survived beyond the specified observational window. Therefore, this method may not be applicable to diseases with high early mortality or low prevalence of exposure. Additionally, the exclusion manner resulted in reduced sample sizes and decreased statistical power. The attractive clone method employed duplications of each participant assigned to each group, ensuring the balanced distribution of both immortal time and covariates between groups, to control ITB and confounding bias, which could be implemented within the framework of the target trial emulation. Due to the violation of the proportional hazard assumption caused by the similarities between groups throughout the observational period, the Cox proportional hazards model was not recommended.[29] Sensitivity analyses with different observational windows were necessary. The RMST results revealed the survival disparity between early-onset exposure groups within the entire population. The artificial doubling of the sample size rendered the precise estimation of variance for the survival difference unattainable. Instead, this estimation was obtained through non-parametric bootstrap replications, and more statistical methodology research was warranted. For the comparison of the statistical capacity among these three methods, simulation was warranted for further exploration.

Nowadays, many investigators or sponsors choose to deposit their data generated from clinical trials into public-available databases.[43] Data from clinical trials, especially those intended for regulatory purposes, comprise extensive patient data, timely follow-up, and high-quality data-management procedures. These clinical trial datasets, and other real-world data resources, could serve as valuable cornerstones for characterizing disease features, identifying prognostic factors, constructing prediction models, and empowering treatment decisions. However, researchers should be aware of the existence and risk of ITB throughout re-utilization. Failure to account for ITB would lead to a substantial overestimation or underestimation of the associ-

Table 2. Hazard ratios (HRs) for the effect of magnesium on progression-free survival (PFS) and overall survival (OS) in joint modelling.

	Model1 [a]			Model2 [a]			Model3 [a]		
	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
OS									
IMpower150	0.72	0.62-0.84	<0.0001	0.71	0.63-0.83	<0.0001	1.03	1.00-1.06	0.0200
IMpower131	0.78	0.70-0.87	<0.0001	0.78	0.70-0.86	<0.0001	1.00	1.00-1.01	0.2782
IMpower130	0.76	0.65-0.91	0.0027	0.76	0.65-0.90	<0.0001	1.04	1.01-1.08	0.0044
OAK	0.98	0.84-1.12	0.7940	0.99	0.85-1.15	0.8687	1.01	1.00-1.01	0.1222
PFS									
IMpower150	0.68	0.57-0.79	<0.0001	0.67	0.59-0.77	<0.0001	1.04	1.02-1.07	<0.0001
IMpower131	0.80	0.72-0.89	0.0027	0.79	0.72-0.88	<0.0001	1.00	1.00-1.01	0.0398
IMpower130	0.76	0.66-0.87	<0.0001	0.77	0.67-0.88	<0.0001	1.01	0.99-1.02	0.3738
OAK	0.90	0.77-1.08	0.2640	0.94	0.79-1.11	0.4533	1.00	1.00-1.01	0.1947

[a] Model 1 estimated the effect of continuous log-transferred standardized serum magnesium on the PFS/OS; model 2 estimated the effect of continuous log-transferred standardized change from baseline serum magnesium on the PFS/OS; model 3 estimated the effect of time-dependent categorical serum magnesium (hypomagnesemia vs. non-hypomagnesemia) on the PFS/OS. The HRs <1 indicated better PFS/OS of higher serum magnesium in model 1 and model 2, the HRs >1 indicated worse PFS/OS of hypomagnesemia in model 3.

Abbreviations: HR: Hazard ratio; OS: overall survival; PFS: progression-free survival.

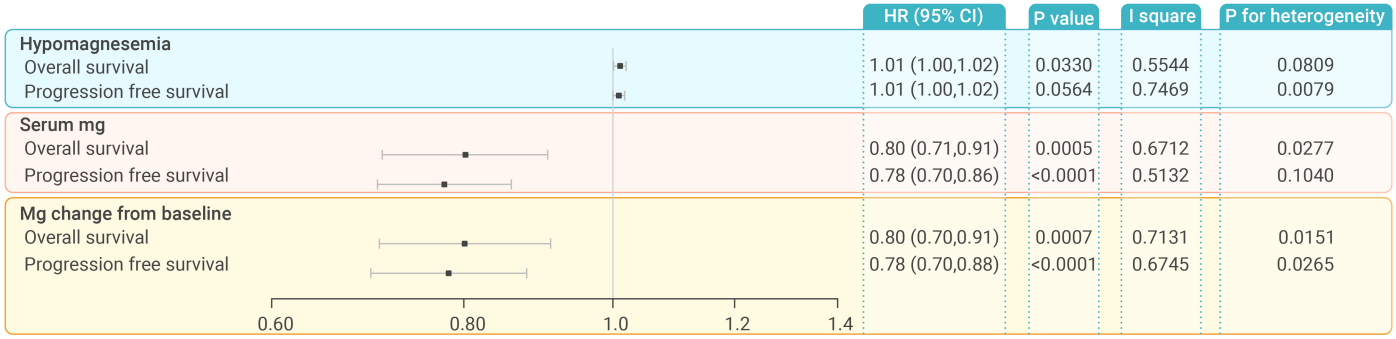

Figure 4. Associations between hypomagnesemia, serum magnesium (mg), and change from baseline serum magnesium, and progression-free survival (PFS) and overall survival (OS) from pooled results using joint modelling of four clinical trials.

ation or effect. We recommend researchers be cautious in grouping participants based on covariates/characteristics generated after the cohort entry/baseline or during treatment. Moreover, the emphasis on defining time zero in the target trial emulation, drawing insights from randomized controlled trial design, aims to mitigate ITB and enhance the quality of evidence derived from real-world research.[30] Prudence in study designs and statistical analysis strategies is crucial to ensure accurate and valid inference on the effects. We advocated the establishment and implementation of guidelines for controlling ITB.

The mechanism of serum magnesium on cancers puzzled scientists. In animals, the pro- and anti-tumor effects could be both observed with inhibition of the primary tumor site and increased metastatic colonization.[27,44] Recently, research has shown that certain magnesium-associated compounds have the potential to prevent metastasis, invasion, and recurrence in cell cancer models, warranting further exploration.[45,46] In subgroup analyses, negative associations were observed between serum magnesium and PFS/OS in all trials involving different metastases, except all different metastatic sites in OAK (Figures S4-S6). In patients with 2+ metastatic sites, significant associations were identified between hypomagnesemia and PFS in IMpower150, and OS in IMpower130 (Figure S6). In the context of first-line treatment for NSCLC, hypomagnesemia has been observed to interact with cancer metastasis. These findings raise the possibility that hypomagnesemia may exert a detrimental influence on tumor progression, particularly in patients with multiple metastases, or that it may be associated with specific patient subpopulations or therapeutic interventions. Further research is needed to investigate the role of serum magnesium in patients with metastases and its potential contribution to cancer metastasis. In Figure 3, landmark analysis in IMpower150 showed a slightly longer OS in the hypomagnesemia group. However, this gap was diminished at 42nd-day and subsequently vanished at 63rd-day landmark (Figures S9-S10). Furthermore, clone-RMST results for IMpower150 showed wide confidence intervals, spanning 23.69 months (-11.58 to 12.11) for PFS, and 81.17 months (-26.30 to 54.87) for OS (Figure S3). In sensitivity analyses, length of confidence intervals was shorter than that of 21-day clone-RMST results [42-day: 22.06 months in PFS and 76.04 months in OS, 63-day: 18.83 months in PFS and 68.36 months in OS, Figures S11-S12]. Thus, the peculiar phenomenon observed in landmark analysis for OS and substantial standard errors of clone-RMST results might suggest the 21-day observational period may not be sufficient to capture the associations. When IPCW was estimated using the pool logistic regression model that accounted for time-varying factors, the sensitivity analysis results were consistent with those from the clone-RMST analysis (Figures S12-S15). Given the notable heterogeneity observed across the studies presented in Figure 4, we conducted an additional subgroup meta-analysis specifically focusing on first-line therapy in NSCLC, incorporating data from IMpower 150, IMpower 130, and IMpower 131. The pooled HRs for serum magnesium levels, change from baseline, and hypomagnesemia were 0.76 (95% CI: 0.70-0.81, I^2=28.3%), 0.75 (95% CI: 0.70-0.81, I^2=47.7%), and 1.02 (95% CI: 1.00-1.04, I^2=83.1%) for PFS, respectively. For OS, the pooled

HRs were 0.76 (95% CI: 0.70-0.82, I²=0.0%), 0.76 (95% CI: 0.70-0.81, I²=0.0%), and 1.02 (95% CI: 1.00-1.04, I²=70.3%) for serum magnesium levels, change from baseline, and hypomagnesemia. The results obtained from this subgroup analysis were consistent with those presented in Figure 4, with reduced heterogeneity observed in trials involving first-line therapy, specifically for serum magnesium levels and change from baseline. This suggests that the line of therapy may be an important source of heterogeneity. However, the relationship between hypomagnesemia and survival continues to necessitate additional research and exploration.

The protective effect of magnesium was reported on the development of different tumors, including liver, pancreatic, and lung cancer.[47-49] Our research supported the merit of serum magnesium in first-line therapy of NSCLC, consistent with that for colorectal cancer patients.[16] Thus, it is critical to proactively prevent the occurrence of hypomagnesemia in cancer patients and promptly manage existing hypomagnesemia with active measures. In clinical practice, prevention and treatment of hypomagnesemia may involve a spectrum of approaches, ranging from oral supplementation with a magnesium-containing solution to intravenous supplementation, with or without anti-cancer treatment interruption. Prospective studies have demonstrated the efficacy and safety of oral and intravenous magnesium supplements for prophylactic effect on hypomagnesemia in cancer patients.[50] Additionally, a randomized study of 32 patients suggested patients with routine intravenous magnesium supplements had higher mean serum magnesium levels compared with those who received magnesium 'as required'.[51] However, there is a dearth of large clinical trials to demonstrate the long-term efficacy and safety of magnesium supplements across treatments for different tumors. To the best of our knowledge, hardly any research has been conducted to report on the association between serum magnesium levels and quality of life. Prior studies have primarily focused on nutritional status and dietary supplements in relation to quality of life in cancer patients.[52,53] Further studies examining the potential benefits of magnesium supplements to improve quality of life are clearly warranted. With prior knowledge, our study and future validation research could contribute to the optimal recognition, prevention, and treatment of hypomagnesemia. In turn, fostering a conducive microenvironment to enhance the benefits derived from anti-cancer treatment.

As of our knowledge, this was the first detailed research on the association of hypomagnesemia and survival in more than 4,000 NSCLC patients. Furthermore, we demonstrated the risk of ITB by grouping patients according to post-therapeutic variables. Three distinct approaches, employing diverse solutions, estimands, and statistical properties, were utilized to address ITB. However, the study had several limitations. Firstly, this post-hoc exploration analysis was conducted without alpha allocation, potentially introducing false-positive results. The consistent results from three trials in first-line therapies lend credibility to this research. Additionally, we noted the detrimental impact of hypomagnesemia, albeit with a small magnitude, as indicated by HRs ranging from 1.00 to 1.04 in joint modelling. However, the effect size of continuous serum magnesium suggests improved survival with higher levels. Moreover, while this analysis aims to evaluate causality, unmeasured and residual confounding may produce false-positive results.

CONCLUSION

In conclusion, addressing ITB in study design and statistical analysis is crucial, especially in observational studies and post-hoc analyses, as this bias could critically affect the validity and reliability of study findings. Three methods were performed and recommended to account for ITB in this research. There was a pressing need to develop guidelines to draw researchers' attention to ITB, which may partially explain the discrepancies in effect estimation. Finally, serum magnesium levels could serve as a potential prognostic biomarker in NSCLC, especially in first-line treatment. Future validation through clinical trials and mechanism research is warranted.

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AUTHOR CONTRIBUTIONS

Y.Z., X.Z., and J.Z. conceptualized and designed the study. Y.Z., J.Z., D.Y., and X.C. applied and got access to the data. J.Z., M.C., and S.W. prepared and analyzed the data. D.Y. and X.C. validated the results. J.Z., D.Y., and M.C. drafted the paper. Y.Z., X.Z., B.P., T.L., H.M., H.S., F.C., and D.C. revised the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

The data that support the findings of this study were provided by the Roche Data Sharing Team and are accessible via the Vivli (https://vivli.org/) platform. However, restrictions apply to the availability of these data, which were used under license for the current study, and are not publicly available.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2025.100124