

Comorbidity Burden and Polypharmacy in Older Patients With Oncogene-Driven NSCLC Receiving Targeted Therapy

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Abstract

Objective:

Evidence regarding the prognostic relevance of comorbidity burden and polypharmacy in older patients with oncogene-driven NSCLC receiving targeted therapy remains limited. We evaluated whether these factors were associated with survival and tumor-control outcomes.

Methods:

We retrospectively analyzed patients aged ≥ 65 years with advanced NSCLC harboring actionable genomic alterations who received targeted therapy at six institutions between 2020 and 2024. Patients were categorized by Charlson Comorbidity Index (CCI; 0–1 vs ≥ 2) and polypharmacy (< 5 vs ≥ 5 medications) and further classified into four combined groups. Overall survival (OS) was the primary endpoint and progression-free survival (PFS) the secondary endpoint.

Results:

Among 609 patients, high CCI was independently associated with worse OS in a multivariable Cox model including both CCI and polypharmacy (HR 1.40, 95% CI 1.05–1.86, $P = 0.021$), whereas polypharmacy was not (HR 1.19, 95% CI 0.93–1.51, $P = 0.165$). Neither CCI nor polypharmacy was independently associated with PFS. Compared with the High/High group, the High/Low (HR 0.56, 95% CI 0.32–0.97), Low/High (HR 0.58, 95% CI 0.40–0.84), and Low/Low groups (HR 0.54, 95% CI 0.38–0.77) had improved OS. Treatment response and major treatment-related toxicities were comparable across groups. In age-stratified analyses, associations appeared stronger among patients aged 65–74 years, although the interaction was not statistically significant ($P = 0.056$).

Conclusion:

Comorbidity burden and polypharmacy provided clinically relevant OS stratification without corresponding differences in PFS, treatment response, or major toxicity. These readily available measures may capture host vulnerability beyond tumor control in older patients receiving targeted therapy.

Introduction

The global population is aging, and more than half of patients diagnosed with lung cancer are aged 65 years or older [1]. Older adults with lung cancer represent a highly heterogeneous population with substantial variability in comorbidities, functional status, medication burden, and treatment tolerance [2] [3]. Consequently, chronological age alone does not adequately reflect physiological reserve or predict

treatment tolerance [4]. Despite recent advances in systemic therapy, optimizing treatment selection and improving clinical outcomes for older adults with lung cancer remain major challenges [5].

To better characterize this heterogeneity, comprehensive geriatric assessment (CGA) and geriatric assessment (GA) have become increasingly important in oncology practice [2][3]. Current ASCO guidelines recommend routine GA for older adults receiving systemic cancer therapy because conventional oncology assessments, including performance status, may fail to identify clinically relevant vulnerabilities [3][6]. Among the GA domains, comorbidity burden and polypharmacy are recognized as important determinants of adverse clinical outcomes in older adults with cancer [3][7].

However, implementation of a full CGA remains challenging in routine clinical practice because it requires considerable time and multidisciplinary resources. Consequently, simpler and more readily available markers of frailty are needed. The Charlson Comorbidity Index (CCI) is one of the most widely used measures of comorbidity burden and has been associated with survival outcomes across various malignancies [8] [9]. Polypharmacy, commonly defined as the concurrent use of five or more medications, has also emerged as a clinically relevant indicator of vulnerability among older patients with cancer [7]. Several studies have suggested that polypharmacy may be associated with poorer survival, increased treatment-related complications, and higher healthcare utilization [7, 10–12].

In non-small cell lung cancer (NSCLC), the prognostic impact of frailty has been demonstrated in patients receiving chemotherapy or immunotherapy, whereas evidence in patients treated with molecularly targeted therapy remains scarce [13–16]. Recent expert recommendations from the International Society of Geriatric Oncology (SIOG) have further emphasized the heterogeneity of older patients with oncogene-driven NSCLC with respect to fitness, comorbidities, and polypharmacy, while highlighting the limited evidence available to guide targeted therapy in this population [17]. A recent meta-analysis reported that frailty was associated with increased mortality and treatment-related toxicity among patients with lung cancer [18]. Nevertheless, the relevance of specific frailty-related domains, including comorbidity burden and polypharmacy, remains incompletely understood in the era of molecularly targeted therapy.

Patients with actionable genomic alterations often experience prolonged survival with targeted therapies, making non-cancer-related factors increasingly important determinants of long-term outcomes [19]. Furthermore, molecularly targeted therapies have demonstrated clinically meaningful efficacy even in vulnerable populations, including older adults and patients with poor performance status [5, 20–25]. While treatment efficacy is largely driven by tumor biology, survival may also be influenced by patient-related factors such as comorbidity burden, medication complexity, and overall physiological reserve. Previous studies have suggested that polypharmacy is associated with poorer outcomes in older patients receiving EGFR-TKIs, and that a high comorbidity burden adversely affects survival in elderly patients with advanced NSCLC [26][27]. However, whether comorbidity burden and polypharmacy independently influence outcomes in older patients with actionable mutation-positive NSCLC treated

with contemporary targeted therapies, and whether their combined assessment provides incremental prognostic value, remains unknown.

Therefore, we conducted a multicenter retrospective study of older patients with actionable mutation-positive NSCLC treated with targeted therapies. We evaluated the prognostic significance of CCI and polypharmacy individually and in combination, with particular focus on their associations with overall survival and progression-free survival.

Methods

Study Design and Patients

This multicenter retrospective study included consecutive patients aged 65 years or older with advanced NSCLC harboring actionable genomic alterations who initiated molecularly targeted therapy between January 2020 and December 2024 at six institutions in Japan. Actionable genomic alterations included EGFR mutations, ALK, ROS1, and RET fusions, MET exon 14 skipping mutations, BRAF V600E mutations, and KRAS G12C mutations. For the primary analyses, patients were categorized into three genomic subgroups: EGFR mutations (EGFR group), ALK/ROS1/RET fusions (Fusion group), and MET exon 14 skipping, BRAF V600E, or KRAS G12C mutations (Other mutation group) [28]. Patients with insufficient baseline information regarding comorbidities or concomitant medications were excluded. Clinical data, including demographic characteristics, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), disease stage, brain metastases, genomic alterations, treatment line, comorbidities, and concomitant medications, were collected from medical records. This study represents a secondary analysis of a previously reported multicenter cohort, addressing a distinct research question regarding the prognostic significance of comorbidity burden and polypharmacy in older patients [28]. This multicenter observational study was conducted per the World Medical Association's Declaration of Helsinki. The study protocol was approved by the institutional review boards of Nippon Medical School (Approval Number:2024 – 246).

Frailty Assessment

Comorbidity burden was assessed using the Charlson Comorbidity Index (CCI) [8]. CCI was calculated based on baseline comorbidities, excluding the index lung cancer; age-related points were not included. Patients were classified into low-CCI (0–1) and high-CCI (≥ 2) groups, consistent with previous oncology studies demonstrating the prognostic value of this cutoff [29]. Polypharmacy was defined as the concurrent use of five or more medications at initiation of targeted therapy and was categorized as low (< 5 medications) or high (≥ 5 medications) [10]. To evaluate the combined impact of comorbidity burden and medication burden, patients were further classified into four groups: Low/Low (CCI 0–1 and polypharmacy < 5), Low/High (CCI 0–1 and polypharmacy ≥ 5), High/Low (CCI ≥ 2 and polypharmacy < 5), High/High (CCI ≥ 2 and polypharmacy ≥ 5).

Outcomes

The primary endpoint was overall survival (OS), defined as the time from initiation of targeted therapy to death from any cause. The secondary endpoint was progression-free survival (PFS), defined as the time from treatment initiation to disease progression or death. Patients were censored at the date of last follow-up if no event had occurred. Objective response rate (ORR) and disease control rate (DCR) were also evaluated according to investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [30]. Safety endpoints included the incidence of any-grade treatment-related ILD/pneumonitis, grade ≥ 3 treatment-related adverse events, treatment discontinuation due to adverse events, and grade 5 adverse events. Adverse events were assessed using Common Terminology Criteria for Adverse Events (CTCAE) in version 5 [31].

Statistical Analysis

Baseline characteristics were compared using Fisher's exact test for categorical variables. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox proportional hazards models including both CCI and polypharmacy were constructed for OS and PFS. Covariates included age group (65–74 vs. ≥ 75 years), sex, smoking history, ECOG PS, treatment line, disease stage, brain metastases, histology and genomic alteration subgroup.

Safety outcomes were compared among frailty groups using Fisher's exact test. Subgroup analyses were performed according to age group (65–74 years and ≥ 75 years). Potential effect modification by age was assessed by including an interaction term between age group and the combined frailty classification in the multivariable Cox proportional hazards model. The global significance of the interaction was evaluated using a likelihood ratio test comparing models with and without the interaction term.

Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R, and R (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided P value < 0.05 . [32].

Results

Patient Characteristics

A total of 609 patients aged ≥ 65 years were included in the analysis. Patient selection is summarized in the study flow diagram (Fig. 1). According to the combined frailty classification, 299 patients (49.1%) were classified as Low/Low, 200 (32.8%) as Low/High, 42 (6.9%) as High/Low, and 68 (11.2%) as High/High. Overall, 316 patients (51.9%) were aged ≥ 75 years, 491 (80.6%) had an ECOG PS of 0–1, and 570 (93.6%) received first-line targeted therapy. Baseline characteristics differed significantly according to frailty classification with respect to age ($P = 0.004$) and ECOG PS ($P = 0.006$), whereas sex, smoking history, disease stage, histology, brain metastases, treatment line, and genomic alteration subgroup were

well balanced across the four groups (Table 1). The distribution of individual genomic alterations and targeted therapies was also comparable among the four frailty groups (Supplementary Table 1).

Table 1
Patient Characteristics

Variable	Overall n (%)	Low/Low (CCI/Poly) n (%)	Low/High (CCI/Poly) n (%)	High/Low (CCI/Poly) n (%)	High/High (CCI/Poly) n (%)	P- value
Total number	609	299	200	42	68	
Age						0.0044
65–74	293 (48.1%)	162 (54.2%)	81 (40.5%)	24 (57.1%)	26 (38.2%)	
≥75	316 (51.9%)	137 (45.8%)	119 (59.5%)	18 (42.9%)	42 (61.8%)	
Sex						0.36
Female	361 (59.3%)	187 (62.5%)	109 (54.5%)	25 (59.5%)	40 (58.8%)	
Male	248 (40.7%)	112 (37.5%)	91 (45.5%)	17 (40.5%)	28 (41.2%)	
ECOG PS						0.0058
0–1	491 (80.6%)	247 (82.6%)	156 (78.0%)	39 (92.9%)	49 (72.1%)	
2–4	110 (18.1%)	46 (15.4%)	43 (21.5%)	2 (4.8%)	19 (27.9%)	
Unknown	8 (1.3%)	6 (2.0%)	1 (0.5%)	1 (2.3%)	0 (0.0%)	
Smoking						0.27
BI < 100	361 (59.3%)	188 (62.9%)	108 (54.0%)	25 (59.5%)	40 (58.8%)	
BI ≥ 100	248 (40.7%)	111 (37.1%)	92 (46.0%)	17 (40.5%)	28 (41.2%)	
Stage						0.27
Recurrence	171 (28.1%)	80(26.8%)	53(26.5%)	14(33.3%)	24(35.3%)	
Data are presented as number (%) unless otherwise indicated. P values were calculated using Fisher's exact test.						
Abbreviations: Ad, adenocarcinoma; ALK, anaplastic lymphoma kinase; BI, Brinkman index; BRAF, B-Raf proto-oncogene; CCI, Charlson Comorbidity Index; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, mesenchymal–epithelial transition; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1.						

Variable	Overall n (%)	Low/Low (CCI/Poly) n (%)	Low/High (CCI/Poly) n (%)	High/Low (CCI/Poly) n (%)	High/High (CCI/Poly) n (%)	P- value
III	29 (4.8%)	12(4.0%)	8(4.0%)	4(9.5%)	5(7.4%)	
IV	409 (67.2%)	207(69.2%)	139(69.5%)	24(57.1%)	39(57.4%)	
Histology						0.98
Ad	589 (96.7%)	288 (96.3%)	194 (97.0%)	41 (97.6%)	66 (97.1%)	
Other	20 (3.3%)	11 (3.7%)	6 (3.0%)	1 (2.4%)	2 (2.9%)	
CNS metastasis						0.12
Yes	177 (29.1%)	98 (32.8%)	56 (28.0%)	10 (23.8%)	13 (19.1%)	
No	432 (70.9%)	201 (67.2%)	144 (72.0%)	32 (76.2%)	55 (80.9%)	
Treatment Line						0.45
1	570 (93.6%)	281 (94.0%)	185 (92.5%)	38 (90.5%)	66 (97.1%)	
≥2	39 (6.4%)	18 (6.0%)	15 (7.5%)	4 (9.5%)	2 (2.9%)	
Gene alteration						
EGFR	515 (84.6%)	254 (84.9%)	171 (85.5%)	33 (78.6%)	57 (83.8%)	
Fusion (ALK/ROS1/RET)	53 (8.7%)	25 (8.4%)	18 (9.0%)	3 (7.1%)	7 (10.3%)	
Other mutation (BRAF/KRAS G12C/MET ex14)	41 (6.7%)	20 (6.7%)	11 (5.5%)	6 (14.3%)	4 (5.9%)	
Data are presented as number (%) unless otherwise indicated. P values were calculated using Fisher's exact test.						
Abbreviations: Ad, adenocarcinoma; ALK, anaplastic lymphoma kinase; BI, Brinkman index; BRAF, B-Raf proto-oncogene; CCI, Charlson Comorbidity Index; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, mesenchymal–epithelial transition; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1.						

Prognostic Impact of CCI and Polypharmacy

In the multivariable Cox proportional hazards model including both CCI and polypharmacy, high CCI (≥ 2) was independently associated with worse OS compared with low CCI (0–1) (HR 1.40, 95% CI 1.05–1.86, $P = 0.021$), whereas polypharmacy was not independently associated with OS (HR 1.19, 95% CI 0.93–1.51, $P = 0.165$). Neither CCI nor polypharmacy was independently associated with PFS (CCI: HR 1.18, 95% CI 0.91–1.52, $P = 0.208$; polypharmacy: HR 0.99, 95% CI 0.81–1.22, $P = 0.939$) (Table 2). Kaplan–Meier analyses showed consistent findings, demonstrating significantly longer OS in the low-CCI group, whereas no significant differences in PFS according to CCI or in OS or PFS according to polypharmacy status were observed (Fig. 2).

Table 2

Multivariable analysis of CCI and Polypharmacy as individual frailty measures for OS and PFS.

OS			
Variable	HR	95% CI	P value
Age (65–74 vs ≥ 75)	0.71	0.56–0.91	0.007
ECOG PS (0–1 vs 2–4)	0.44	0.33–0.59	< 0.001
Sex (Female vs Male)	1.00	0.76–1.32	0.997
Smoking status (BI < 100 vs BI ≥ 100)	0.68	0.51–0.91	0.009
Treatment line (1 vs ≥ 2)	0.53	0.32–0.86	0.010
Stage (Recurrence or III vs IV)	0.31	0.24–0.41	< 0.001
CNS metastasis (Negative vs Positive)	0.64	0.49–0.82	< 0.001
Histology (Ad vs non-Ad)	0.65	0.32–1.32	0.231
Gene: Fusion vs EGFR	0.25	0.14–0.47	< 0.001
Other mutation vs EGFR	1.25	0.75–2.08	0.401
CCI (High vs Low)	1.40	1.05–1.86	0.021
Polypharmacy (High vs Low)	1.19	0.93–1.51	0.165
PFS			
Variable	HR	95% CI	P value
Age (65–74 vs ≥ 75)	0.85	0.69–1.04	0.116
ECOG PS (0–1 vs 2–4)	0.52	0.40–0.67	< 0.001
Sex (Female vs Male)	0.81	0.64–1.01	0.065
Smoking status (BI < 100 vs BI ≥ 100)	0.76	0.60–0.96	0.019
Treatment line (1 vs ≥ 2)	0.46	0.31–0.68	< 0.001
Stage (Recurrence or III vs IV)	0.45	0.36–0.55	< 0.001
Multivariable Cox proportional hazards models were constructed to evaluate the independent associations of Charlson Comorbidity Index (CCI) and polypharmacy with overall survival (OS) and progression-free survival (PFS). Covariates included age, ECOG performance status, sex, smoking status, treatment line, disease stage, central nervous system metastasis, histology and genomic alteration subgroup.			
Abbreviations: Ad, adenocarcinoma; BI, Brinkman index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PS, performance status.			

OS			
Variable	HR	95% CI	P value
CNS metastasis (Negative vs Positive)	0.73	0.59–0.90	0.004
Histology (Ad vs non-Ad)	0.42	0.25–0.70	0.001
Gene: Fusion vs EGFR	0.29	0.19–0.46	< 0.001
Other mutation vs EGFR	1.39	0.93–2.08	0.106
CCI (High vs Low)	1.18	0.91–1.52	0.208
Polypharmacy (High vs Low)	0.99	0.81–1.22	0.939
Multivariable Cox proportional hazards models were constructed to evaluate the independent associations of Charlson Comorbidity Index (CCI) and polypharmacy with overall survival (OS) and progression-free survival (PFS). Covariates included age, ECOG performance status, sex, smoking status, treatment line, disease stage, central nervous system metastasis, histology and genomic alteration subgroup.			
Abbreviations: Ad, adenocarcinoma; BI, Brinkman index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PS, performance status.			

Prognostic Impact of Combined Frailty Assessment

Kaplan–Meier analyses demonstrated significant differences in OS among the four frailty groups, whereas no significant difference in PFS was observed (Fig. 3). In multivariable analysis using the High/High group as the reference category, all three other frailty groups were independently associated with improved OS: High/Low (HR 0.56, 95% CI 0.32–0.97, $P = 0.040$), Low/High (HR 0.58, 95% CI 0.40–0.84, $P = 0.004$), and Low/Low (HR 0.54, 95% CI 0.38–0.77, $P < 0.001$) (Table 3). Treatment response was generally comparable across frailty groups. ORR was comparable across the four frailty groups (77.3%, 71.5%, 73.8%, and 66.2%, respectively; $P = 0.21$). Although DCR differed significantly (92.3%, 85.5%, 85.7%, and 83.8%, respectively; $P = 0.035$), the absolute differences were modest (Supplementary Table 2).

Table 3
Multivariable Cox proportional hazards analyses of the combined frailty classification for OS.

OS			
Variable	HR	95% CI	P value
Age (65–74 vs ≥ 75)	0.73	0.57–0.94	0.013
ECOG PS (0–1 vs 2–4)	0.44	0.33–0.60	< 0.001
Sex (Female vs Male)	0.98	0.74–1.30	0.900
Smoking status (BI < 100 vs BI ≥ 100)	0.69	0.52–0.92	0.011
Treatment line (1 vs ≥ 2)	0.53	0.33–0.86	0.010
Stage (Recurrence or III vs IV)	0.31	0.24–0.41	< 0.001
CNS metastasis (Negative vs Positive)	0.63	0.49–0.81	< 0.001
Histology (Ad vs non-Ad)	0.68	0.33–1.38	0.283
Gene: Fusion vs EGFR	0.25	0.13–0.47	< 0.001
Other mutation vs EGFR	1.31	0.78–2.21	0.305
CCI/Poly: High/Low vs High/High	0.56	0.32–0.97	0.040
CCI/Poly: Low/High vs High/High	0.58	0.40–0.84	0.004
CCI/Poly: Low/Low vs High/High	0.54	0.38–0.77	< 0.001
65–74 OS			
Variable	HR	95% CI	P value
ECOG PS (0–1 vs 2–4)	0.50	0.32–0.79	0.003
Sex (Female vs Male)	1.07	0.72–1.59	0.750
Smoking status (BI < 100 vs BI ≥ 100)	0.78	0.52–1.17	0.233
Treatment line (1 vs ≥ 2)	0.56	0.30–1.06	0.076
Multivariable Cox proportional hazards analyses of overall survival (OS) were performed in the overall cohort and according to age group (65–74 years and ≥ 75 years). Covariates included age group (overall cohort only), ECOG performance status, sex, smoking status, treatment line, disease stage, central nervous system metastasis, histology, genomic alteration subgroup, and combined frailty classification. The High/High group (CCI ≥ 2 and polypharmacy ≥ 5 medications) was used as the reference category for the combined frailty classification. The global interaction between age group and combined frailty classification did not reach statistical significance (P for interaction = 0.056).			
Abbreviations: Ad, adenocarcinoma; BI, Brinkman index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PS, performance status.			

OS			
Variable	HR	95% CI	P value
Stage (Recurrence or III vs IV)	0.42	0.29–0.62	< 0.001
CNS metastasis (Negative vs Positive)	0.62	0.44–0.88	0.007
Histology (Ad vs non-Ad)	0.60	0.21–1.68	0.326
Gene: Fusion vs EGFR	0.24	0.11–0.52	< 0.001
Other mutation vs EGFR	1.29	0.59–2.84	0.527
CCI/Poly: High/Low vs High/High	0.28	0.14–0.60	< 0.001
CCI/Poly: Low/High vs High/High	0.41	0.23–0.72	0.002
CCI/Poly: Low/Low vs High/High	0.32	0.19–0.55	< 0.001
≥ 75 OS			
Variable	HR	95% CI	P value
ECOG PS (0–1 vs 2–4)	0.42	0.28–0.63	< 0.001
Sex (Female vs Male)	0.93	0.62–1.41	0.748
Smoking status (BI < 100 vs BI ≥ 100)	0.61	0.40–0.92	0.020
Treatment line (1 vs ≥ 2)	0.48	0.22–1.05	0.068
Stage (Recurrence or III vs IV)	0.22	0.14–0.33	< 0.001
CNS metastasis (Negative vs Positive)	0.59	0.40–0.86	0.006
Histology (Ad vs non-Ad)	0.64	0.23–1.79	0.391
Gene: Fusion vs EGFR	0.37	0.13–1.02	0.054
Other mutation vs EGFR	1.37	0.67–2.79	0.383
CCI/Poly: High/Low vs High/High	1.29	0.56–2.99	0.551
Multivariable Cox proportional hazards analyses of overall survival (OS) were performed in the overall cohort and according to age group (65–74 years and ≥ 75 years). Covariates included age group (overall cohort only), ECOG performance status, sex, smoking status, treatment line, disease stage, central nervous system metastasis, histology, genomic alteration subgroup, and combined frailty classification. The High/High group (CCI ≥ 2 and polypharmacy ≥ 5 medications) was used as the reference category for the combined frailty classification. The global interaction between age group and combined frailty classification did not reach statistical significance (P for interaction = 0.056).			
Abbreviations: Ad, adenocarcinoma; BI, Brinkman index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PS, performance status.			

OS			
Variable	HR	95% CI	P value
CCI/Poly: Low/High vs High/High	0.73	0.45–1.20	0.217
CCI/Poly: Low/Low vs High/High	0.74	0.45–1.22	0.234
Multivariable Cox proportional hazards analyses of overall survival (OS) were performed in the overall cohort and according to age group (65–74 years and ≥ 75 years). Covariates included age group (overall cohort only), ECOG performance status, sex, smoking status, treatment line, disease stage, central nervous system metastasis, histology, genomic alteration subgroup, and combined frailty classification. The High/High group (CCI ≥ 2 and polypharmacy ≥ 5 medications) was used as the reference category for the combined frailty classification. The global interaction between age group and combined frailty classification did not reach statistical significance (P for interaction = 0.056).			
Abbreviations: Ad, adenocarcinoma; BI, Brinkman index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PS, performance status.			

Age-Specific Analyses

In exploratory age-stratified analyses, the association between combined frailty classification and OS appeared more pronounced among patients aged 65–74 years than among those aged ≥ 75 years (Table 3; Fig. 4). Among patients aged 65–74 years, compared with the High/High group, the High/Low (HR 0.28, 95% CI 0.14–0.60, $P < 0.001$), Low/High (HR 0.41, 95% CI 0.23–0.72, $P = 0.002$), and Low/Low groups (HR 0.32, 95% CI 0.19–0.55, $P < 0.001$) were independently associated with improved OS. In contrast, no significant association was observed among patients aged ≥ 75 years (High/Low: HR 1.29, 95% CI 0.56–2.99, $P = 0.551$; Low/High: HR 0.73, 95% CI 0.45–1.20, $P = 0.217$; Low/Low: HR 0.74, 95% CI 0.45–1.22, $P = 0.234$). The global interaction between age group and combined frailty classification did not reach statistical significance (P for interaction = 0.056).

Safety

Safety outcomes according to frailty classification are summarized in Supplementary Table 3. Higher rates of grade ≥ 3 adverse events and treatment discontinuation were numerically observed in the Low/High and High/High groups, although these differences were not statistically significant. The incidence of grade ≥ 3 adverse events was 22.1%, 27.5%, 23.8%, and 25.0% in the Low/Low, Low/High, High/Low, and High/High groups, respectively ($P = 0.579$). Treatment discontinuation due to adverse events occurred in 29.8%, 37.0%, 28.6%, and 38.2% of patients, respectively ($P = 0.254$). The incidence of ILD/pneumonitis was comparable across groups (10.4%, 14.0%, 11.9%, and 14.7%, respectively; $P = 0.549$). A single treatment-related grade 5 ILD/pneumonitis event occurred in the Low/Low group.

Discussion

In this multicenter retrospective study of older patients with actionable mutation-positive NSCLC treated with targeted therapies, we demonstrated that a simple frailty assessment integrating comorbidity burden and polypharmacy provided clinically meaningful prognostic information. When CCI and polypharmacy were simultaneously included in the multivariable model, higher CCI remained independently associated with worse OS, whereas polypharmacy alone was not. The combined frailty classification further stratified OS after adjustment for established prognostic factors. Importantly, these associations were observed predominantly for OS rather than PFS, suggesting that comorbidity burden and medication burden may capture host-related vulnerability beyond tumor control.

Current ASCO guidelines recommend geriatric assessment (GA) for older adults receiving systemic anticancer therapy, and several prospective studies have demonstrated the benefits of GA-guided interventions [3, 33, 34]. In Japan, the prospective ENSURE-GA study (NEJ041/CS-Lung001) showed that standardized GA with structured interventions improved patient-centered outcomes in older patients with lung cancer [35, 36]. Nevertheless, comprehensive GA requires considerable time, multidisciplinary expertise, and institutional resources, limiting its implementation in routine oncology practice. Our findings suggest that two routinely available clinical variables, comorbidity burden and medication burden, may provide a pragmatic approach to identifying vulnerable patients, particularly when comprehensive GA is not feasible [2]. Importantly, the independent prognostic value of CCI after simultaneous adjustment for polypharmacy and established clinical prognostic factors, including ECOG performance status, suggests that clinically relevant vulnerability is not fully captured by conventional oncology assessments or medication burden alone. These findings further support the importance of comprehensive geriatric assessment in older adults with cancer, while suggesting that simple frailty measures may serve as practical alternatives when formal geriatric assessment is not routinely available.

Several previous studies have reported associations between frailty-related factors and outcomes in NSCLC. Similarly, Hakozaiki et al. demonstrated that polypharmacy was independently associated with poorer survival among older patients with EGFR-mutant NSCLC receiving EGFR-TKIs, suggesting that medication burden remains clinically relevant even in the era of targeted therapy [26]. Our findings extend these observations by examining a broader population of patients with actionable genomic alterations treated with contemporary targeted therapies. To our knowledge, this is the first study to demonstrate that the combined assessment of comorbidity burden and polypharmacy provided additional prognostic stratification beyond either factor considered individually. Because PFS, ORR, and severe treatment-related toxicities were largely comparable across frailty groups, vulnerable older adults may still derive substantial benefit from molecularly targeted therapies despite greater comorbidity burden or medication use [20–24]. In our previous study of patients with T790M-positive NSCLC, osimertinib was feasible even in an older and clinically vulnerable population, although poor performance status remained associated with inferior survival outcomes [25]. Therefore, frailty-related factors alone should not necessarily preclude the use of molecularly targeted therapy when otherwise clinically indicated.

A key strength of the present study is its focus on patients with actionable mutation-positive NSCLC receiving molecularly targeted therapies. In oncogene-driven NSCLC, treatment efficacy is largely determined by oncogenic dependency and drug activity, allowing host-related determinants of prognosis to be evaluated with less confounding by differences in antitumor efficacy [19, 28]. This setting provided a unique opportunity to evaluate the prognostic impact of frailty independent of treatment efficacy. The discordance between OS and tumor-control outcomes is noteworthy. Although OS differed substantially according to frailty classification, PFS, ORR, and major safety outcomes were largely comparable across groups. These findings suggest that the association between frailty-related factors and OS is unlikely to be explained solely by differences in the efficacy or tolerability of the initial targeted therapy. Instead, comorbidity burden and medication burden may reflect broader host-related vulnerabilities, including reduced physiological reserve, competing health risks, non-cancer mortality, and differences in post-progression management. This interpretation is particularly plausible in oncogene-driven NSCLC, where prolonged disease control frequently increases the relative contribution of non-cancer-related factors to overall survival.

Interestingly, the association between combined frailty classification and OS appeared substantially more pronounced among patients aged 65–74 years than among those aged ≥ 75 years. Although the formal interaction test did not reach conventional statistical significance, the P value for interaction of 0.056, together with the markedly different effect estimates between the two age groups, suggests possible age-related heterogeneity in the prognostic relevance of frailty. Several explanations may account for this observation. First, chronological age itself may become a dominant determinant of prognosis among very old patients, attenuating the relative contribution of individual frailty markers. Second, clinicians may already tailor treatment intensity and supportive care more carefully in patients aged ≥ 75 years, thereby reducing differences attributable to frailty status. Alternatively, frailty assessment may be particularly informative among patients aged 65–74 years, in whom chronological age alone may fail to identify clinically relevant vulnerability. Notably, most prospective geriatric oncology studies, including the Japanese ENSURE-GA study, have primarily focused on patients aged ≥ 75 years [36]. These findings raise the possibility that frailty screening may also be clinically relevant in the “young-old” population and warrant further investigation. Nevertheless, given the exploratory nature of the subgroup analyses and the absence of a statistically significant interaction, these findings should be interpreted cautiously and considered hypothesis-generating.

As treatment strategies for oncogene-driven NSCLC incorporate increasingly complex combinations and prolonged sequences [37, 38] [39–41], host-related vulnerability may become more relevant to treatment tolerability and long-term outcomes.

Several limitations should be acknowledged. First, this was a retrospective observational study, and residual confounding cannot be excluded despite multivariable adjustment. Baseline differences among frailty groups may not have been fully captured by the available clinical variables. Second, because the study was designed to evaluate prognostic associations, it remains difficult to distinguish whether frailty primarily influenced survival itself or altered treatment-related factors that subsequently affected

outcomes. Third, detailed treatment-related variables, including dose reductions, treatment interruptions, relative dose intensity, subsequent lines of therapy, and supportive care interventions, were not systematically evaluated. These factors may partly explain the observed differences in OS despite similar PFS and response outcomes. In addition, cause-specific mortality and post-progression treatment were not systematically collected; therefore, we could not determine whether the observed discordance between OS and PFS was attributable to competing non-cancer mortality, reduced access to subsequent therapy, or other post-progression factors. Fourth, CCI and polypharmacy represent only selected dimensions of frailty and cannot replace comprehensive geriatric assessment. Fifth, the age-stratified analyses were exploratory and may have been underpowered, particularly in the High/Low subgroup. Although the interaction test suggested possible age-related heterogeneity, it did not reach conventional statistical significance. In addition, this study was based on a partially overlapping multicenter cohort that has been previously reported; however, the present analysis addressed a distinct research question focusing on frailty-related prognostic factors [28]. Finally, although this study included a large multicenter cohort of older patients with actionable mutation-positive NSCLC, the findings should be considered hypothesis-generating and require prospective validation.

In conclusion, a combined assessment of comorbidity burden and polypharmacy provided meaningful prognostic information in older patients with actionable mutation-positive NSCLC treated with targeted therapies. While frailty-related factors were associated with OS, their associations with PFS, treatment response, and major toxicities were limited. These findings suggest that simple frailty measures may capture host-related vulnerabilities beyond tumor control and may complement ongoing efforts to integrate geriatric assessment into routine lung cancer care.

Declarations

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CRedit authorship contribution statement:

Yasuhiro Kato: Conceptualization, Data curation, Methodology, Formal analysis, Investigation, Writing – original draft.

Tetsuya Okano: Methodology, Formal analysis, Writing – review & editing.

Nobuhiko Nishijima: Data curation, Investigation, Writing – review & editing.

Satoshi Takahashi: Data curation, Investigation, Writing – review & editing.

Yukari Shirakura: Data curation, Investigation, Writing – review & editing.

Miwako Omori: Data curation, Investigation, Writing – review & editing.

Maiko Asai: Data curation, Investigation, Writing – review & editing.

Aya Fukuizumi: Investigation, Methodology, Writing – review & editing.

Shinji Nakamichi: Investigation, Methodology, Writing – review & editing.

Susumu Takeuchi: Investigation, Methodology, Writing – review & editing.

Kazuo Kasahara: Supervision, Writing – review & editing.

Masahiro Seike: Supervision, Writing – review & editing.

All authors critically reviewed the manuscript for important intellectual content and approved the final version of the manuscript.

Declaration of competing interests:

Yasuhiro Kato has received lecture honoraria from AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Amgen and Merck.

Tetsuya Okano has received lecture honoraria from AstraZeneca, Eli Lilly, Pfizer, Chugai Pharmaceutical, Boehringer Ingelheim, and Merck Biopharma.

Satoshi Takahashi has received lecture honoraria from AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Takeda, Pfizer, and Amgen.

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Maiko Asai reports that a family member is employed by Novartis.

Nobuhiko Nishijima, Yukari Shirakura, Miwako Omori, and Aya Fukuizumi declare no competing interests.

Ethics approval: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Nippon Medical School Hospital (Approval No. 2024-246).

Consent to Participate: The requirement for individual informed consent was waived because of the retrospective nature of the study, with an opt-out approach used in accordance with institutional policy.

Consent for publication: Consent for publication was obtained in accordance with institutional policies.

Data availability statement: The datasets generated and/or analyzed during the current study are not publicly available because of patient privacy and institutional data-sharing restrictions but are available from the corresponding author on reasonable request, subject to approval by the relevant institutional review boards and participating institutions.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Figures

Figure 1

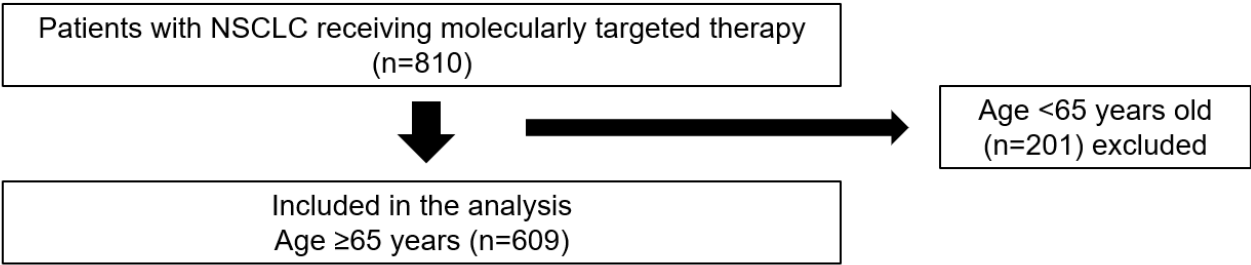


Figure 1

Patient selection flow diagram. 609 patients aged ≥65 years were included in the present analysis

Figure 2

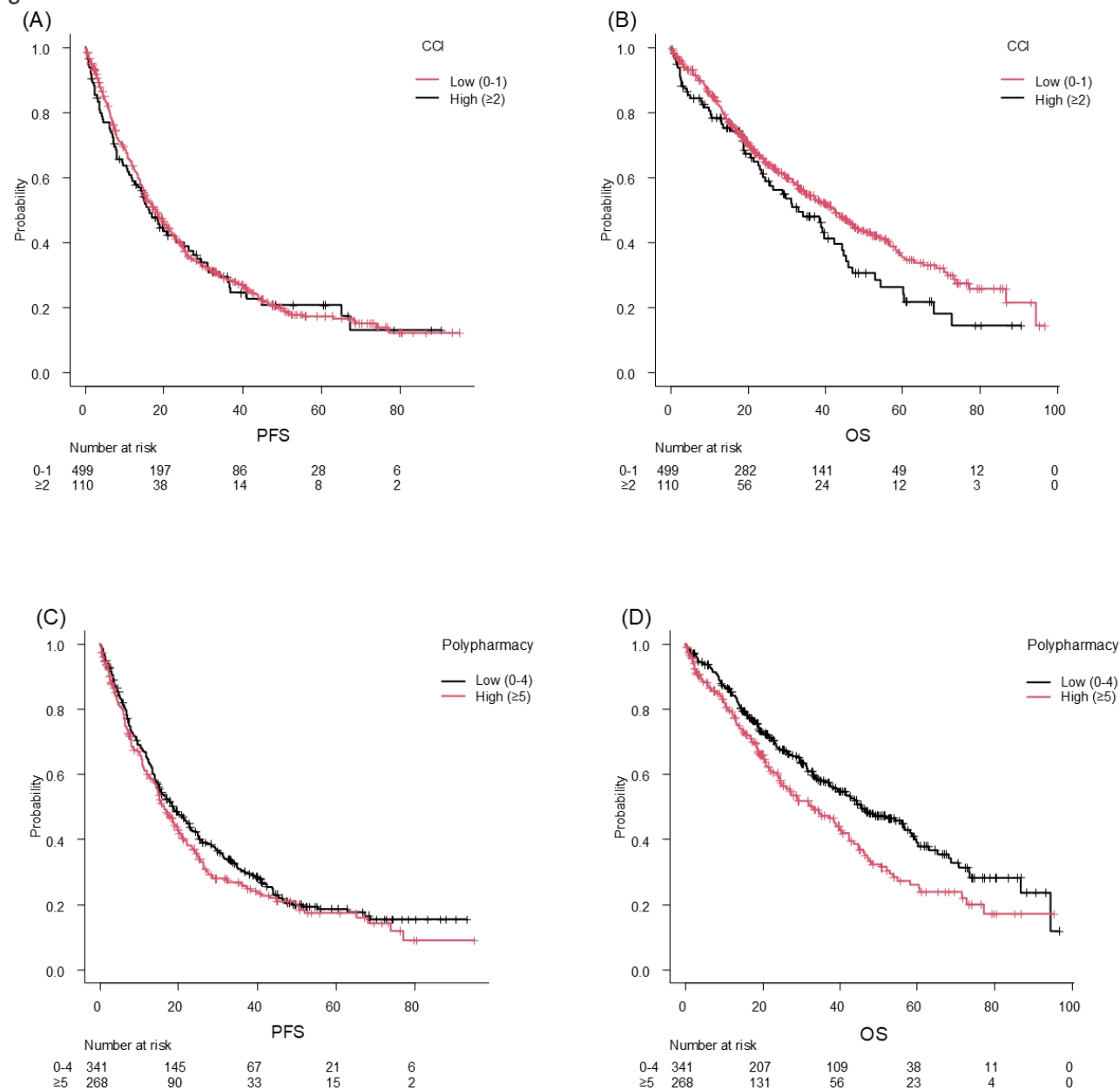


Figure 2

Kaplan–Meier curves according to Charlson Comorbidity Index and polypharmacy.

(A) PFS according to CCI. (B) OS according to CCI. (C) PFS according to polypharmacy.

(D) OS according to polypharmacy. Kaplan–Meier curves for overall survival (OS) and progression-free survival (PFS) according to Charlson Comorbidity Index (CCI; low [0–1] vs. high [≥ 2]) and polypharmacy (low [<5 medications] vs. high [≥ 5 medications]).

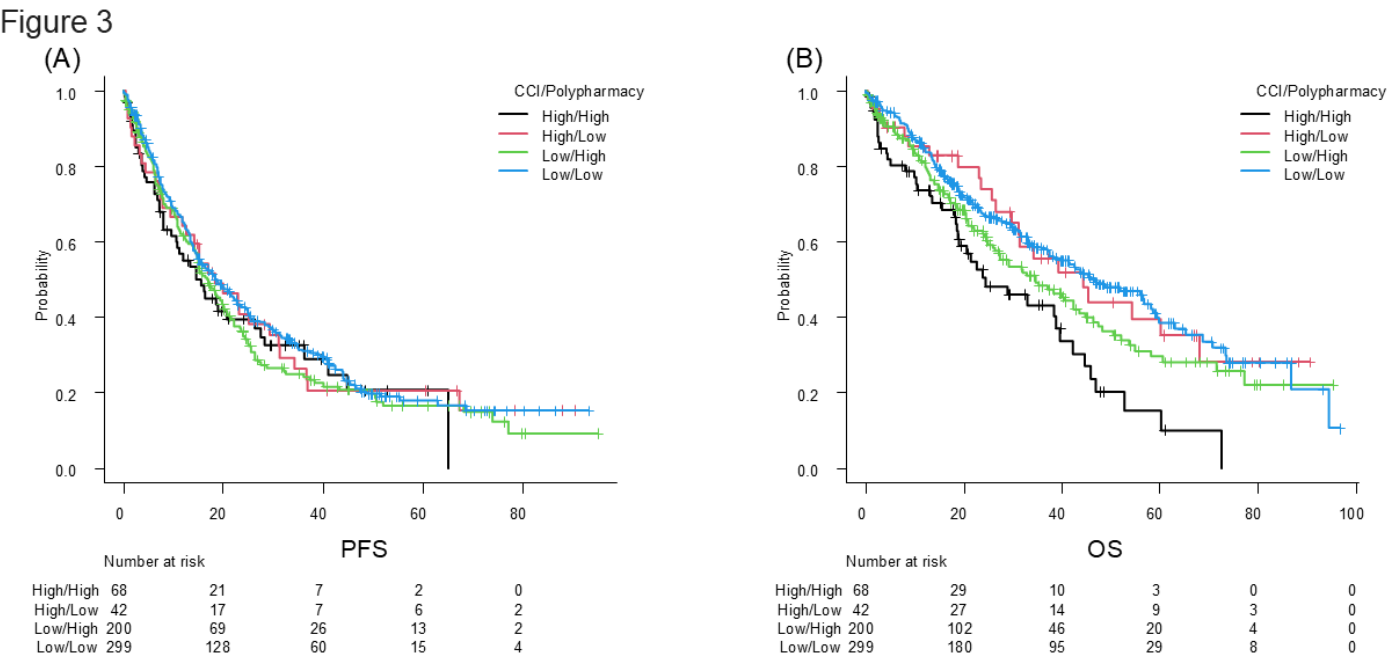


Figure 3

Kaplan–Meier curves according to the combined frailty classification.

Kaplan–Meier curves for (A) progression-free survival and (B) overall survival according to the combined frailty classification: Low/Low (CCI 0–1 and <5 medications), Low/High (CCI 0–1 and ≥ 5 medications), High/Low (CCI ≥ 2 and <5 medications), and High/High (CCI ≥ 2 and ≥ 5 medications).

Figure 4

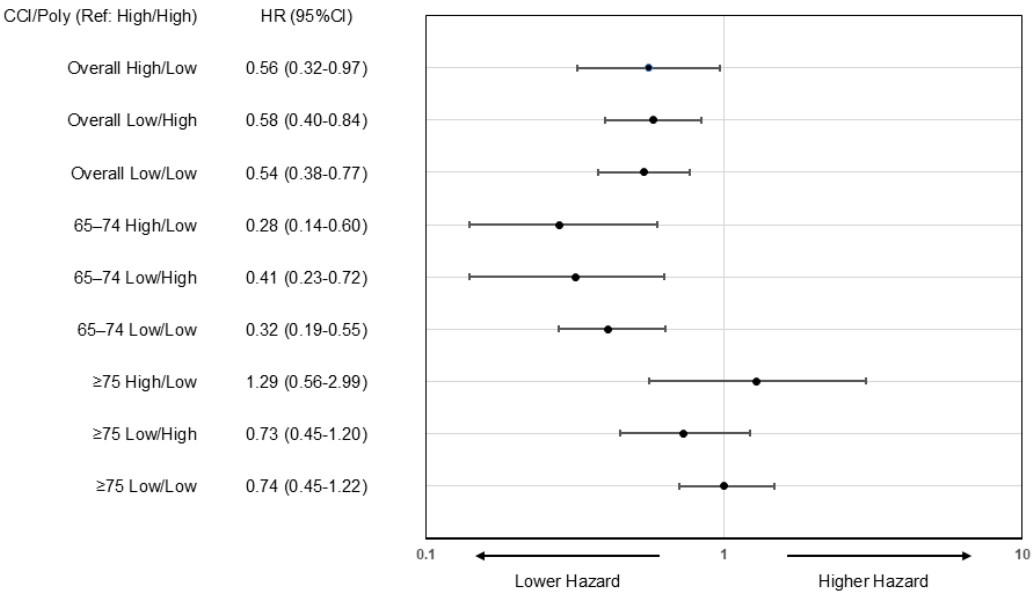


Figure 4

Forest plot of multivariable Cox proportional hazards analyses for overall survival in the overall cohort and according to age group. Hazard ratios (HRs) and 95% confidence intervals (CIs) are shown for each combined CCI/polypharmacy group, with the High/High group as the reference.