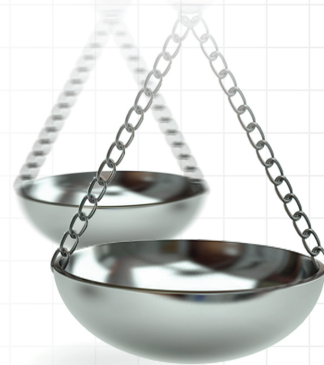




Factors affecting treatment selection and overall survival for first-line EGFR-tyrosine kinase inhibitor therapy in non-small-cell lung cancer

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Aim: To investigate the factors associated with treatment selection and overall survival for first-line EGFR-tyrosine kinase inhibitors (EGFR-TKIs) therapy among patients with non-small-cell lung cancer. **Materials & methods:** We conducted a retrospective cohort study of linked administrative health databases in Ontario, Canada. **Results:** A total of 1011 patients received an EGFR-TKI as first-line therapy. Treatment selection and overall survival associated with these treatments were affected by age, sex, geographical residency, comorbidities and different sites of metastasis. **Conclusion:** Though recent approval of osimertinib offers a potential new standard of care in the first-line setting, earlier generation TKIs remain pillars in treatment of non-small-cell lung cancer therapeutic armamentarium. Our findings may contribute to optimizing treatment sequencing of EGFR-TKIs to maximize clinical benefits.

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Lung cancer is a leading cause of cancer-related death worldwide [1]. In 2018, estimates suggested a total of 1.76 million persons died of lung cancer, accounting for 18.4% of all cancer-related deaths [2]. Approximately 85% of all lung cancer cases are non-small-cell lung cancer (NSCLC) [3]. The 5-year survival rate for lung cancer ranges between 13 and 20% [4,5]. Most patients are diagnosed in advanced stages of NSCLC, which results in poor prognosis [6].

Advancements in our understanding of cancer biology have allowed us to tailor treatment approaches based on patients' genetic profiles. A half of NSCLC cases are associated with known mutations, and several actionable gene alterations have been identified for targeted treatment [7–9]. EGFR has been one of the most prevailing targets for devising specific treatment algorithms for patients with NSCLC. Approximately 15% of NSCLC cases have an activating mutation in the EGFR genes in exon 18–21 [10]. Those harboring EGFR mutations are eligible to receive EGFR-tyrosine kinase inhibitors (EGFR-TKIs), which have been demonstrated to improve objective response rates and progression-free survival compared with conventional chemotherapy in first-line settings [11–23].

There are currently five EGFR-TKIs approved as first-line treatment for NSCLC in Canada, including the first-generation TKIs erlotinib (Tarceva; Hoffman-La Roche, Basel, Switzerland) and gefitinib (Iressa; AstraZeneca, London, UK), second-generation TKIs afatinib (Giotrif; Boehringer Ingelheim, Ingelheim, Germany) and dacomitinib (Vizimpro; Pfizer, NY, USA), and third-generation TKI osimertinib (Tagrisso; AstraZeneca, London, UK).

Currently, a dearth of clinical evidence exists to suggest whether one EGFR-TKI should be chosen over another in a typical first-line setting [24,25]. This suggests multiple factors could affect treatment selection, though a delineation of these factors in the case of EGFR-TKIs has never been undertaken. Previous research has identified general factors related to prescribing decisions, for example, treatment sequencing, evidence from clinical trials, safety/toxicity

profiles associated with each agent, growing familiarity with new agents among practitioners, regional/institutional preference, reimbursement and influence of pharmaceutical companies [26,27], though the applicability of these factors to EGFR-TKIs is unknown.

While several randomized controlled trials and observational studies have estimated the efficacy/effectiveness of prognostic factor-guided EGFR-TKIs in advanced/metastatic EGFR mutation-positive NSCLC population [11–23,28–35], limited information is available on the longitudinal effects of EGFR-TKIs at the population level. Furthermore, evidence regarding the comparative effectiveness of these EGFR-TKIs is inconsistent across the literature.

To our knowledge, no studies thus far have investigated how prescribing decisions for EGFR-TKIs are made and the factors that may affect these prescribing decisions. Using population-based administrative health datasets, we sought to determine which factors influence the receipt of certain EGFR-TKIs in first-line settings and investigate how these are associated with overall survival (OS). Due to the recency of the approval dates and concomitant lack of data for dacomitinib and osimertinib, the present study only pertained to afatinib, erlotinib and gefitinib.

Materials & methods

Study design

This was a retrospective, population-based cohort study of linked health administrative data in Ontario, Canada. The datasets are housed at the Institute for Clinical Evaluative Sciences (ICES), a prescribed entity under Ontario's Personal Health Information Protection Act. The Act authorizes ICES to draw individual patient-level data from multiple health administrative datasets for researchers to use in secondary analyses. The research was cleared for ethics by the Office of Research Ethics at the University of Waterloo (ORE # 41067).

Study population

The study included all patients diagnosed with NSCLC in Ontario between 01 January 2010 and 31 August 2019. NSCLC cases were identified through the Ontario Cancer Registry (OCR). The International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes 34.0–34.9, in combination with relevant histology codes for nonsquamous, squamous and not otherwise specified were used to identify cases of primary lung cancer from the OCR. Inclusion criteria were age ≥ 18 years at diagnosis, locally advanced or metastatic NSCLC, and receipt of afatinib, erlotinib or gefitinib as first-line treatment. We excluded persons with death dates on or before the date of NSCLC diagnosis, and individuals who received more than one EGFR-TKI as first-line treatment. The dataset did not contain any information on biomarker status; thus, we assumed patients with records of EGFR-TKI prescription in the first-line setting had positive EGFR mutation status.

Data sources

Multiple health administrative datasets were linked using encrypted unique identifiers. The OCR contains information on incident cancer cases and patients who have died of cancer in Ontario since 1964 [36,37]. The OCR includes data on date and stage of NSCLC diagnosis, age, sex, geographical location, rural versus urban residence and date of death. The Registered Persons Database contains demographic information and vital statistics on all residents of Ontario who are eligible for universal healthcare coverage in the province. The Canadian Institute for Health Information – Discharge Abstract Database contains data on diagnoses and procedures for all hospitalizations in Ontario. The Ontario Drug Benefits (ODB) database contains data on all prescription medications dispensed to those eligible for publicly funded drug coverage. These include all persons aged ≥ 65 years, persons living in homes for special care and long-term care homes, persons receiving professional services through the home and community care service programs, persons receiving social assistance, and persons receiving benefits through Trillium Drug Program, a scheme which helps people with high prescription drug costs relative to their net household income. The ODB does not capture information covered by private insurance and compassionate supplies from manufacturers. The Activity Level Reporting system contains information on all systemic and radiation therapy services and outpatient oncology clinic visits.

Covariates

We searched the literature and consulted expert opinion to identify several sociodemographic and clinical factors that may influence treatment selection and OS [24,38–44]. These factors included: year of diagnosis, age, sex,

rurality, neighborhood income quintile, local health integration network (LHIN), clinical stage, histology, Charlson comorbidity index and sites of metastasis (bone, brain, liver and lung).

Neighborhood household income was determined through linkage of postal codes to Canadian census data and stratified into three tertiles, with the first and last tertiles representing neighborhoods with the lowest and highest income status, respectively. Charlson comorbidity index was determined from hospitalization data utilizing a 2-year 'look-back' window, with the score from the most recently available hospitalization record applied to each participant [40,41]. We followed Stavem *et al.*'s approach and considered missing comorbidities to be absent [45]. At the time of data collection, publicly funded healthcare services in Ontario were administered on a regional basis by 14 LHINs, each with its own distinct geographical territory. Recently, Ontario integrated these LHINs into five regions consisting of North, West, Toronto Central, East and South regions. The analyses were conducted reflective of these changes.

Statistical analysis

All variables were categorical and described using frequencies and percentages. To explore the factors associated with treatment selection, we conducted two separate logistic regression analyses comparing afatinib to gefitinib and erlotinib to gefitinib. We used gefitinib as the reference category because it was the most established treatment group among the three EGFR-TKIs; erlotinib and gefitinib have been in use since 2010, while afatinib was approved for use and publicly funded in 2014. Furthermore, while erlotinib is only publicly funded for second- and third-line settings in Ontario, it is indicated for first-line setting as well. The aim of our models was not to predict treatment selection, but to identify which variables may be of importance to clinicians prescribing EGFR-TKIs for first-line treatment. Therefore, our focus was not to identify the most parsimonious model, but rather to build an explanatory model and examine the effects of all relevant covariates on treatment selection.

A priori, we defined sociodemographic and clinical factors that may be important in clinical decision making for treatment selection and its associated outcomes (see 'Covariates' above) [24,38–44]. A series of chi-square tests were conducted to test the associations between independent variables and the outcome variable. In addition, all explanatory variables were checked for multicollinearity using variance inflation factors. Discrimination of the models was assessed with the area under the receiver operating characteristic curve (AUC). Calibration of the models was evaluated using the Hosmer–Lemeshow goodness-of-fit tests.

OS was assessed using the Kaplan–Meier method on the overall population and various patient subgroups. The OS was calculated from the date of diagnosis of NSCLC to death (for any reason) or the last day of patient follow-up (censored). Comparisons between groups were performed using the log-rank test. Multivariable Cox proportional hazards models were used to determine adjusted hazard ratios (aHRs) and to evaluate the predictive factors for survival. Statistical significance was set at $\alpha = 0.05$. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., NC, USA).

Results

A total of 88,179 patients were identified as having a primary diagnosis of lung cancer in the OCR between 2010 and 2019. Of these, 68,334 were NSCLC cases and 33,321 had stage IIIB/IV NSCLC. In total, 1011 patients met the eligibility criteria and were enrolled in the study (Table 1); 67 patients were excluded as they had records of receiving more than one EGFR-TKI in the first-line setting (Figure 1). A total of 110 (10.9%) patients received afatinib, while 482 (47.7%) and 419 (41.4%) received erlotinib and gefitinib, respectively. Male patients constituted 41.8% of the study population. Almost all patients had nonsquamous histology (98.7%) and no patients had squamous cell carcinoma. The majority of patients were at stage IV NSCLC (89.8%) at the time of diagnosis.

Treatment selection

The results of the logistic regression analyses are presented in Table 2. We found no evidence of multicollinearity between explanatory variables. The goodness-of-fit of the models were confirmed (Hosmer–Lemeshow: chi-square = 7.29 and $p = 0.50$ for gefitinib vs erlotinib; chi-square = 8.33 and $p = 0.40$ for gefitinib vs afatinib) and the models exhibited moderate discriminatory capacity (AUC = 0.75 for gefitinib vs erlotinib; AUC = 0.69 for gefitinib vs afatinib).

Age was associated with prescribing choice of EGFR-TKIs, with older patients more likely to be prescribed gefitinib over afatinib and erlotinib. Compared with patients aged 18–59 years, the adjusted odds ratio (aOR)

Table 1. Baseline patient sociodemographic and clinical characteristics.

Variables	Afatinib n = 110 (%)	Erlotinib n = 482 (%)	Gefitinib n = 419 (%)	Total n = 1011 (%)	p-value
Year of diagnosis					<0.0001
– 2010–2014	6 (5.4%)	425 (88.2%)	178 (42.5%)	609 (60.2%)	
– 2015–2019	104 (94.6%)	57 (11.8%)	241 (57.5%)	402 (39.8%)	
Age, years					<0.0001
– 18–59	36 (32.7%)	126 (26.1%)	84 (20.1%)	246 (24.3%)	
– 60–69	15 (13.6%)	85 (17.6%)	53 (12.7%)	153 (15.1%)	
– 70–79	55 (50.0%)	247 (51.3%)	217 (51.8%)	519 (51.3%)	
– 80+	4 (3.6%)	24 (5.0%)	65 (15.5%)	93 (9.2%)	
Sex					<0.0001
– Males	44 (40.0%)	245 (50.8%)	134 (32.0%)	423 (41.8%)	
– Females	66 (60.0%)	237 (49.2%)	285 (68.0%)	588 (58.2%)	
Rurality					0.20
– Rural	15 (13.6%)	65 (13.5%)	41 (9.8%)	121 (12.0%)	
– Urban	95 (86.4%)	417 (86.5%)	378 (90.2%)	890 (88.0%)	
Neighborhood income quintile					0.27
– 1 (poorest)	57 (51.8%)	208 (43.2%)	167 (39.9%)	432 (42.7%)	
– 2	16 (14.6%)	86 (17.8%)	78 (18.6%)	180 (17.8%)	
– 3 (wealthiest)	37 (33.6%)	188 (39.0%)	174 (41.5%)	399 (39.5%)	
LHIN					<0.0001
– North	11 (10.3%)	30 (6.3%)	17 (4.1%)	58 (5.8%)	
– West	27 (25.2%)	150 (31.4%)	84 (20.4%)	261 (26.2%)	
– Toronto	9 (8.4%)	33 (6.9%)	55 (13.3%)	97 (9.7%)	
– Central	34 (31.8%)	89 (18.6%)	168 (40.8%)	291 (29.2%)	
– East	26 (24.3%)	176 (36.8%)	88 (21.4%)	290 (29.1%)	
Clinical stage					0.06
– IIIB	11 (10.0%)	60 (12.4%)	32 (7.6%)	103 (10.2%)	
– IV	99 (90.0%)	422 (87.6%)	387 (92.4%)	908 (89.8%)	
Histology					0.33
– Nonsquamous	109 (99.1%)	478 (99.2%)	411 (98.1%)	998 (98.7%)	
– Squamous cell	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
– NOS	1 (0.9%)	4 (0.8%)	8 (1.9%)	13 (1.3%)	
CCI					0.25
– No	107 (97.3%)	452 (93.8%)	400 (95.5%)	959 (94.9%)	
– Yes	3 (2.7%)	30 (6.2%)	19 (4.5%)	52 (5.1%)	
Sites of metastasis					
– Liver	16 (14.6%)	66 (13.7%)	44 (10.5%)	126 (12.5%)	0.27
– Bone	40 (36.4%)	150 (31.1%)	167 (39.9%)	357 (35.3%)	0.02
– Brain	26 (23.6%)	66 (13.7%)	98 (23.4%)	190 (18.8%)	0.0004
– Lung	19 (17.3%)	121 (25.1%)	101 (24.1%)	241 (23.8%)	0.22

CCI: Charlson comorbidity index; LHIN: Local health integration network; NOS: Not otherwise specified.

for prescribing afatinib in lieu of gefitinib in patients aged ≥ 80 years was 0.14 (95% CI: 0.04–0.42), and 0.19 (95% CI: 0.10–0.34) for erlotinib versus gefitinib. A larger proportion of patients aged ≥ 70 years received gefitinib over the other two drugs. Erlotinib was more commonly prescribed for male patients than gefitinib (aOR: 2.59; 95% CI: 1.90–3.52).

Regional prescribing preferences were evident. Patients residing in LHIN – North region, compared with Toronto Central, were less likely to be prescribed gefitinib than afatinib and erlotinib. The adjusted odds of receiving afatinib was 3.30-times greater than receiving gefitinib (95% CI: 1.02–10.64), while the adjusted odds was 2.57-times greater for erlotinib versus gefitinib (95% CI: 1.15–5.75). In the West and East regions, erlotinib

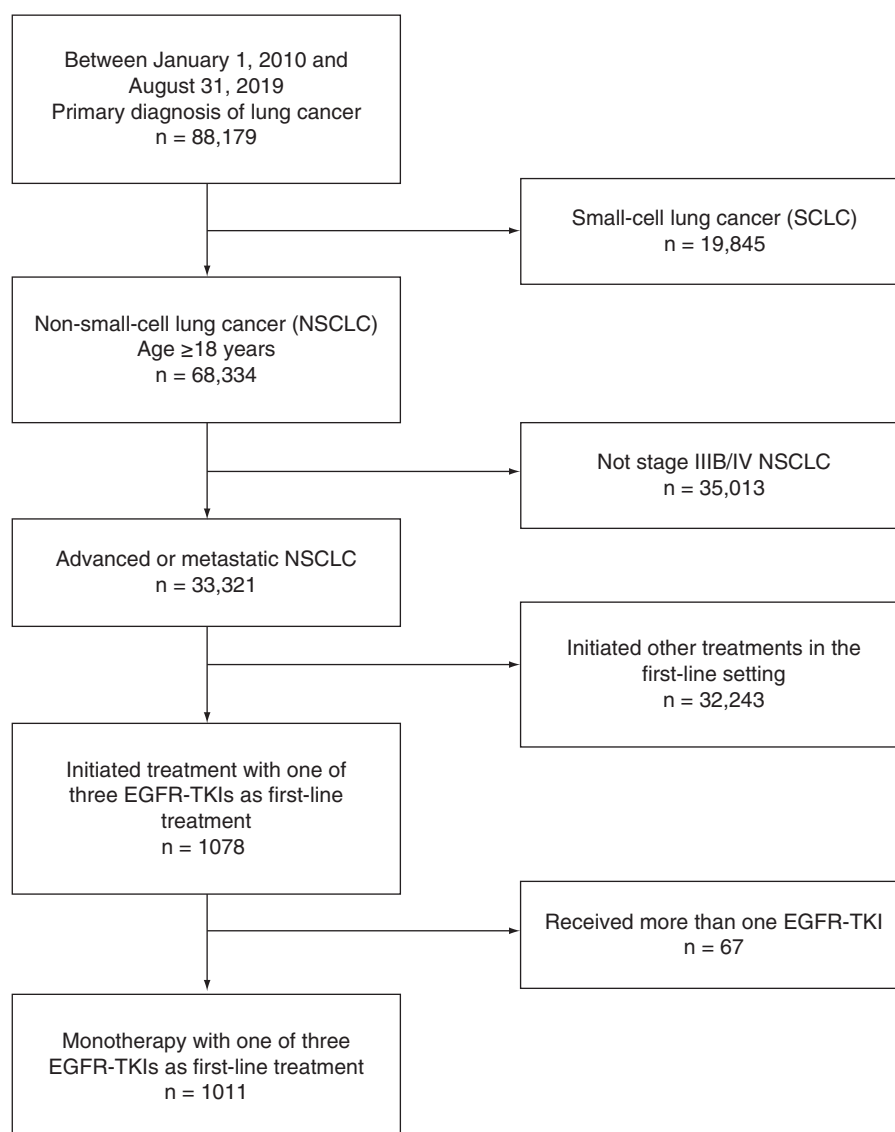


Figure 1. Flow diagram of patient selection.
NSCLC: Non-small-cell lung cancer; TKI: Tyrosine kinase inhibitors.

was more commonly prescribed over afatinib and gefitinib. The adjusted odds of being prescribed erlotinib in the West region was 2.94 (95% CI: 1.68–5.14) and 3.51 (95% CI: 2.01–6.11) in the East region.

We found associations between sites of metastasis and prescribing decisions. Patients with metastasis to bone and brain were less likely to be prescribed erlotinib than gefitinib. Among patients with bone metastasis, the aOR for erlotinib prescription was 0.58 (95% CI: 0.42–0.80) and 0.53 (95% CI: 0.36–0.78) for patients with brain metastasis. Erlotinib was more commonly prescribed for patients with liver metastasis than gefitinib (aOR: 1.74; 95% CI: 1.10–2.78).

Survival analysis

The median OS of the overall cohort was 19.53 months (95% CI: 18.38–20.75; [Figure 2](#)). Statistically significant differences in OS were observed across the EGFR-TKIs; the median OS were 31.04 (95% CI: 23.41–42.05), 17.36 (95% CI: 16.04–18.48) and 21.63 months (95% CI: 19.27–23.18) for afatinib, erlotinib and gefitinib, respectively ([Figure 3A](#)). Significantly shorter OS was observed in patients who were male (median: 17.33 months; 95% CI: 16.01–18.97; p for log-rank test = 0.0017; [Figure 3C](#)), had presence of comorbidities (15.81 months; 95% CI: 13.32–20.52; p for log-rank test = 0.026; [Figure 3H](#)), and had metastasis to liver (16.27 months; 95% CI: 14.14–

Table 2. Adjusted odds ratios for prescription of afatinib and erlotinib compared with gefitinib.

Variable	Afatinib, OR (95% CI) (n = 110)	Erlotinib, OR (95% CI) (n = 482)	Gefitinib (reference) (n = 419)
Age, years			
– 18–59	1	1	1
– 60–69	0.83 (0.40–1.73)	1.12 (0.69–1.83)	1
– 70–79	0.66 (0.39–1.12)	0.73 (0.50–1.06)	1
– 80+	0.14 (0.04–0.42)	0.19 (0.10–0.34)	1
Sex			
– Males	1.43 (0.89–2.27)	2.59 (1.90–3.52)	1
– Females	1	1	1
Rurality			
– Rural	1.10 (0.52–2.31)	0.98 (0.60–1.59)	1
– Urban	1	1	1
Neighborhood income quintile			
– 1 (poorest)	1.53 (0.78–2.97)	1.07 (0.71–1.63)	1
– 2	1	1	1
– 3 (wealthiest)	0.94 (0.47–1.87)	0.98 (0.64–1.48)	1
LHIN			
– North	3.30 (1.02–10.64)	2.57 (1.15–5.75)	1
– West	2.03 (0.86–4.82)	2.94 (1.68–5.14)	1
– Toronto	1	1	1
– Central	1.03 (0.45–2.34)	0.73 (0.42–1.26)	1
– East	1.66 (0.70–3.95)	3.51 (2.01–6.11)	1
Clinical stage			
– IIIB	1.70 (0.75–3.85)	1.43 (0.84–2.44)	1
– IV	1	1	1
CCI			
– No	1.58 (0.44–5.68)	0.81 (0.42–1.59)	1
– Yes	1	1	1
Bone metastasis			
– Yes	0.78 (0.47–1.29)	0.58 (0.42–0.80)	1
– No/unknown	1	1	1
Liver metastasis			
– Yes	1.58 (0.78–3.20)	1.74 (1.10–2.78)	1
– No/unknown	1	1	1
Brain metastasis			
– Yes	1.14 (0.67–1.97)	0.53 (0.36–0.78)	1
– No/unknown	1	1	1
Lung metastasis			
– Yes	0.64 (0.36–1.16)	1.37 (0.96–1.95)	1
– No/unknown	1	1	1

CCI: Charlson comorbidity index; LHIN: Local health integration network; OR: Odds ratio.

18.44; p for log-rank test = 0.0001; Figure 3I) and bone (17.98 months; 95% CI: 16.21–20.38; p for log-rank test = 0.0094; Figure 3J). Furthermore, shorter median OS was observed in older patients, but the difference was not statistically significant.

A multivariable Cox regression model showed that prescription of erlotinib (aHR: 1.58; 95% CI: 1.33–1.86; $p < .0001$), aged ≥ 80 years (aHR: 1.42; 95% CI: 1.07–1.88; $p = 0.02$), presence of comorbidities (aHR: 1.37; 95% CI: 1.01–1.86; $p = 0.04$), liver metastasis (aHR: 1.49; 95% CI: 1.22–1.83; $p = 0.0001$), bone metastasis (aHR: 1.31; 95% CI: 1.13–1.53; $p = 0.0004$) and brain metastasis (aHR: 1.30; 95% CI: 1.07–1.57; $p = 0.007$) were inversely associated with OS (Table 3). Prescription of afatinib (aHR: 0.61; 95% CI: 0.45–0.82; $p = 0.0013$)

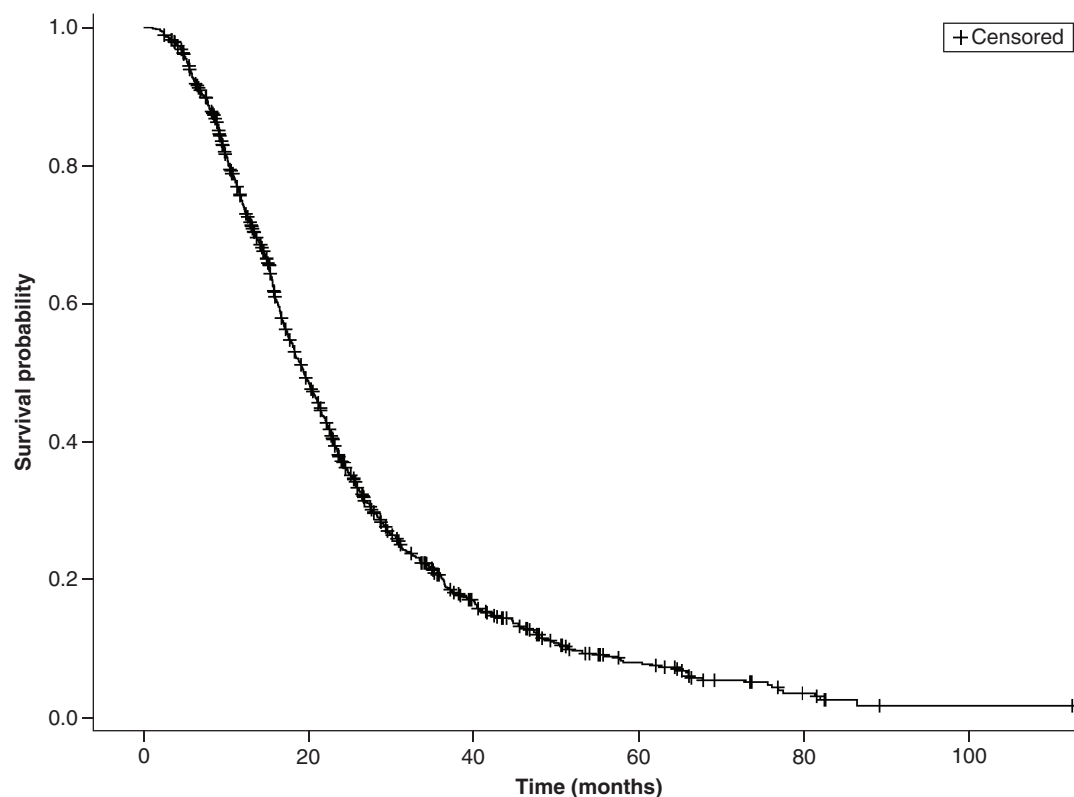


Figure 2. Overall survival for the entire study population.

was positively associated with OS (Table 3).

Discussion

We identified sociodemographic and clinical factors influencing treatment selection and OS among patients who received EGFR-TKIs between 2010 and 2019. Compared with gefitinib, erlotinib was prescribed more frequently for those who were males, residing in certain geographical locations (North, West and East regions), and had liver metastasis. The results for afatinib were similar; while a higher prescription of afatinib was noted among patients with no comorbidities and had brain metastasis, the results were not statistically significant. Compared with afatinib and erlotinib, gefitinib was more commonly prescribed for older patients and those with bone metastasis. We found type of EGFR-TKI therapy, age, presence of comorbidities, and metastasis to liver, bone and brain as potential independent prognostic factors for OS.

We expected to find some of the associations reported in Tables 2 and 3. Previous studies showed that brain metastasis was an independent prognostic factor for progression-free survival and OS [46,47]. Among patients with EGFR mutation, the incidence of brain metastasis can be as large as one in two persons [48]. The use of afatinib is widely accepted for patients with brain metastasis due to improved capacity for blood–brain barrier penetration into the intracranial lesions to initiate antitumor activities compared with reversible EGFR-TKIs [49,50].

In terms of the use of gefitinib for patients with bone metastasis, previous studies suggested that gefitinib may reduce bone metastasis growth through inhibition of EGF signaling pathways in bone stromal cells and improve pathologic fractures [51,52]. Furthermore, the high usage of gefitinib in older patients may partly be explained by the safety/toxicity profile of afatinib over erlotinib and gefitinib. While results from the noninterventional RealGiDo study indicated that adverse events (AEs) with afatinib can be managed with dose adjustments and care measures [53], older patients may not be able to handle the intensity of AEs associated with afatinib. For patients with terminal NSCLC, the intent of treatment would likely focus on health-related quality of life, which involves minimizing treatment-related AEs and managing symptoms.

Another factor to consider is acquired resistance, the most common being the development of a T790M mutation, which occurs in 50–70% of cases [54–56]. Studies have shown that afatinib is able to overcome acquired

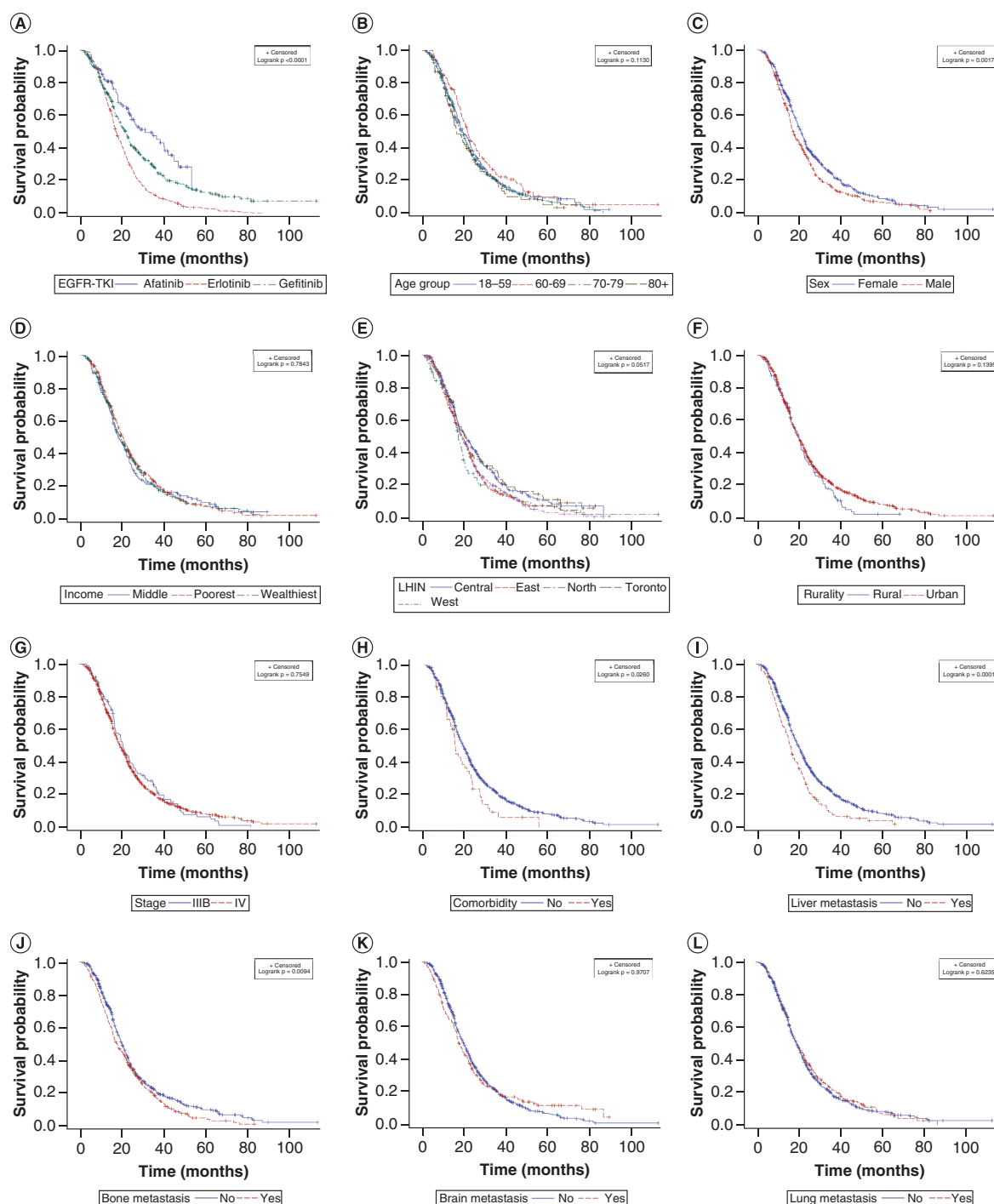


Figure 3. Overall survival by patient factors. Overall survival according to treatment (afatinib, erlotinib or gefitinib) (A); age groups (B); sex (C); income (D); geographical residency (E); rural versus urban (F); clinical stage (G); presence of comorbidity (H); liver metastasis (I); bone metastasis (J); brain metastasis (K); and lung metastasis (L).

first-generation EGFR-TKI resistance [57,58]; therefore, afatinib may have been reserved for subsequent use in later lines for patients who fail previous EGFR-TKI therapy. Although afatinib is not publicly funded for second-line settings in Ontario, funding of afatinib for patients who have initiated another EGFR-TKI therapy in the first-line setting, and who have not had disease progression, are considered on a case-by-case basis.

Table 3. Multivariable Cox regression of overall survival.

Variable	HR (95% CI)	p-value
EGFR-TKI		
– Afatinib	0.61 (0.45–0.82)	0.0013
– Erlotinib	1.58 (1.33–1.86)	<0.0001
– Gefitinib	Ref	
Age		
– 18–59	Ref	
– 60–69	0.86 (0.68–1.08)	0.18
– 70–79	1.15 (0.96–1.37)	0.13
– 80+	1.42 (1.07–1.88)	0.02
Sex		
– Males	1.14 (0.99–1.32)	0.08
– Females	Ref	
Rurality		
– Urban	Ref	
– Rural	1.05 (0.84–1.30)	0.67
Clinical stage		
– IIIB	1.05 (0.83–1.34)	0.68
– IV	Ref	
CCI		
– No	Ref	
– Yes	1.37 (1.01–1.86)	0.04
Income		
– Poorest	Ref	
– Middle	1.09 (0.90–1.32)	0.40
– Wealthiest	1.04 (0.89–1.21)	0.67
LHIN		
– North	1.35 (0.92–1.97)	0.12
– West	1.13 (0.86–1.48)	0.40
– Toronto	Ref	
– Central	1.05 (0.81–1.37)	0.72
– East	1.15 (0.88–1.50)	0.30
Liver metastasis		
– No	Ref	
– Yes	1.49 (1.22–1.83)	0.0001
Bone metastasis		
– No	Ref	
– Yes	1.31 (1.13–1.53)	0.0004
Brain metastasis		
– No	Ref	
– Yes	1.30 (1.07–1.57)	0.007
Lung metastasis		
– No	Ref	
– Yes	0.94 (0.80–1.11)	0.48

CCI: Charlson comorbidity index; HR: Hazards ratio; LHIN: Local health integration network; Ref: Reference; TKI: Tyrosine kinase inhibitor.

Our median OS estimate stratified by EGFR-TKIs are inconsistent with what was reported in several trials [11–23]. The median OS observed in our study for erlotinib and gefitinib were shorter than what was observed in most published trials. Exception was the results reported in the IPASS trial, where median OS was 18.8 months for gefitinib [11]. However, the median OS of afatinib observed in our study was longer than what was reported in Phase IIb Lux-Lung 7 trial (27.9 months), Phase III Lux-Lung 3 (28.2 months) and Lux-Lung 6 (23.1 months) trials [20,59].

The differences in median OS between EGFR-TKIs were consistent with other observational studies that reported effectiveness of EGFR-TKIs in clinical practice [28–35]. Most studies reported higher median OS for afatinib over erlotinib and gefitinib [29,31,33]. However, Li and colleagues reported higher median OS for patients who received erlotinib (23.2 months) than afatinib (20.7 months) [32]. In addition, Chao and colleagues reported substantially higher median OS for patients who received erlotinib (34.6 months) than gefitinib (19.2 months) [28].

Given the fact that 15% of patients with nonsquamous histology harbor EGFR mutation, we had expected a larger sample for our study. However, the relatively small sample size could be attributed to the initial challenges in implementation of biomarker testing in Ontario in the early 2010s, along with logistical difficulties, for example, delayed turnaround times, which led chemotherapy to be used as the first-line treatment to avoid clinical deterioration [60,61]. A previous study has suggested approximately one in four patients do not undergo biomarker testing [62]. Furthermore, the ODB database captured only information related to publicly-funded medications; therefore, prescription medications covered by private insurance and compassionate supplies from manufacturers could not be considered.

An interesting finding of this study was that only 38.9% of our study cohort initiated a second-line therapy, which questions the notion of reserving therapies for subsequent use (e.g., development of acquired T790M mutation resistance) to maximize the duration of chemotherapy-free treatment. The results from the Phase III FLAURA trial demonstrated superior efficacy and safety profiles associated with osimertinib compared with first-generation TKIs in the first-line setting, regardless of T790M mutational status [63]. In terms of treatment sequencing, patients receiving osimertinib as first-line treatment would not receive any subsequent EGFR-TKIs upon progression and would likely involve treatments with platinum doublets or immune checkpoint inhibitors. Therefore, clinical challenges remain in deciding whether the most effective therapy should be used as first-line treatment or be reserved for later lines to expand treatment options.

The strength of our study was the linkage and use of population-based administrative datasets, which captured all relevant data and complete follow-up for all patients. To our knowledge, this was the first study to systematically assess the factors influencing prescribing decisions associated with EGFR-TKIs using administrative datasets. Nonetheless, our study has limitations. First, the number of patients who received afatinib was relatively small compared with patients who received erlotinib and gefitinib, due to later approval of afatinib. The difference in sample size resulting from the late licensing date may have contributed to selection and length-time bias in our study, which may have caused overestimation of odds ratios and survival estimates in our analyses. The OS data for persons who received erlotinib and gefitinib were more mature compared with persons who received afatinib. In addition, previous studies have demonstrated the importance of Eastern Cooperative Oncology Group performance status and the type of EGFR mutation status, for example, exon 19 deletion (Exon19DEL) and the exon 21 codon 858 point mutation (L858R), as important factors to consider in treatment selection and survival [20,64–70]. However, a lack of data on Eastern Cooperative Oncology Group performance status and EGFR mutation status prohibited us from carrying out any analyses involving these factors. We assumed that patients who received any of the three EGFR-TKIs had positive EGFR mutation, regardless of the type. Although highly unlikely, we cannot rule out the possibility that TKIs may have been prescribed to EGFR wild-type patients. Lastly, since the ODB database did not capture information on private insurance claims and compassionate supplies, we were not able to assess prescribing differences based on types of insurance.

Conclusion

The results of the present study demonstrated that factors including age, sex, geographical residency, and metastasis to bone, liver and brain were independent factors influencing treatment selection of EGFR-TKIs. Presences of comorbidities, in addition to the aforementioned factors, were independent prognostic factors for OS. In clinical practice, there were significant differences in OS between the three EGFR-TKIs. Additional population-based studies are required to compare the clinical effectiveness of EGFR-TKIs stratified by EGFR-mutation status.

Summary points

- Factors affecting treatment selection and overall survival (OS) of first-line EGFR-tyrosine kinase inhibitors remain unclear.
- We conducted a retrospective, population-based cohort study linking non-small-cell lung cancer cases identified in the Ontario Cancer Registry between 2010 and 2019 to other administrative health databases.
- The outcomes of interest for this study were prescription of one of three EGFR-tyrosine kinase inhibitors (afatinib, erlotinib and gefitinib) and OS.
- Logistic regression models were conducted to evaluate the associations between treatment selection and patient characteristics.
- The Kaplan–Meier method was used to estimate OS; multivariable Cox regression analyses were performed to test the associations between OS and patient characteristics.
- A total of 1011 patients met the inclusion/exclusion criteria.
- The median OS were 31.04 (95% CI: 23.41–42.05), 17.36 (95% CI: 16.04–18.48), and 21.63 months (95% CI: 19.27–23.18) for afatinib, erlotinib and gefitinib, respectively.
- Age, sex, geographical residency and sites of metastasis affected treatment selection.
- Prescription of erlotinib or gefitinib, older age, presence of comorbidities, and metastasis to bone, liver and brain were poor prognostic factors associated with OS.

Author contributions

Y-J Kim, M Oremus, HH Chen and S Horton were responsible for study conception and design. Y-J Kim, M Oremus and D Fearon were responsible for data analysis. Y-J Kim, M Oremus, HH Chen, T McFarlane, D Fearon and S Horton revised and approved final manuscript for publication.

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Data sharing statement

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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