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Original article

Eligibility of real-world patients with metastatic breast cancer for clinical trials

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ABSTRACT

Introduction: The results of clinical trials in metastatic breast cancer (MBC) are generalized to real-world patients. This study determines the proportion of real-world patients who would be eligible for clinical trials and compares outcomes in eligible versus ineligible patients.
Methods: Patients diagnosed with MBC from 2004 to 2015 in a large Canadian province were included. Patients with one of the following criteria were considered ineligible: the presence of comorbid conditions (anemia, uncontrolled diabetes, heart disease, liver disease, and kidney disease) or a history of immunosuppression or prior malignancy. The likelihood of receiving cancer therapy was analysed using logistic regression models and factors affecting overall survival (OS) were assessed by Cox proportional hazards models.
Results: A total of 1585 patients with MBC were identified. The median age at diagnosis was 63 years. Of these, 512 (32.3%) patients were deemed ineligible in whom the two most common reasons for ineligibility were renal dysfunction (17.2%), and previous immunosuppression (7.8%). In the real world, ineligible patients were less likely to receive chemotherapy (29.5% vs 45.8%; $P < 0.001$) but not radiation treatment (7.6% vs 9.6%; $P = 0.196$) or hormonal therapy (57.6% vs 60.6%; $P = 0.261$). The 5-year OS of ineligible patients who received systemic therapy in the real-world was significantly better than those who did not.
Conclusions: Despite being ineligible for clinical trials based on common eligibility criteria, many real-world patients receive systemic treatment and derive possible benefit. Broadening of inclusion criteria in clinical trials will enhance the representation of real-world patients and increase the generalizability of results.

1. Introduction

Clinical trials in oncology continue to be the gold standard for evaluating the efficacy of novel interventions in the era of evidence-based medicine [1]. Over the past decade, clinical trials have contributed to the optimization of treatment strategies, approval of novel drugs, and improvements in the quality of life and survival of patients with cancer [2,3]. However, the inclusion and exclusion criteria employed to enrol patients in clinical trials have increasingly been criticized for being overly strict. This practice leads to poor generalizability of results to the real-world cancer population [4] [–] [6].

Failing to meet the stringent eligibility criteria represents one of the major barriers for patients to participate in clinical trials [7]. Previous studies using different study approaches have demonstrated that as many as 80% of real-world patients may be ineligible to participate in clinical trials [6] [–] [10]. The common reasons cited for ineligibility include advanced age and the presence of specific comorbid conditions such as cardiovascular disease, hepatic dysfunction, and chronic kidney failure [6,8]. This contrasts the demographics of real-world patients with cancer who tend to be older and who are more likely to have comorbid conditions than their younger counterparts [11]. Such discordance leads to gaps in evidence when treating many patients with cancer [12]. For instance, most clinical trials exclude older adults or anyone with significant comorbid conditions even though a fair proportion of

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Abbreviations

MBC	Metastatic Breast Cancer
OS	Overall Survival
CSS	Cancer-specific survival
ACR	Alberta Cancer Registry
ICD	International Classification of Diseases
VIF	Variance inflation factor
OR	Odds ratio
CI	Confidence interval
SHR	Subdistribution hazard ratio
HR	Hazard ratio

patients encountered in routine clinical practice would fit into these groups [6,8].

Clinical trials conducted in patients with metastatic breast cancer have caused a paradigm shift in treatment strategies and resulted in significant improvement in overall survival (OS) [13] [–] [15]. However, metastatic breast cancer continues to be an incurable disease and it remains the leading cause of cancer-related deaths among women [16]. Systemic therapy, including hormones, chemotherapy and targeted agents, forms the backbone of treatment whereas radiotherapy is indicated as a palliative measure to control symptoms, most commonly affecting the bone and brain [17,18].

This study aimed to identify the proportion of real-world patients with metastatic breast cancer considered clinical ineligible and to characterize the reasons for their ineligibility. Further, we planned to determine the treatment patterns of the ineligible group in the real-world setting and analyse the effect of treatment on OS and cancer-specific survival (CSS) in this subpopulation of patients.

2. Materials and methods

2.1. Study design and data sources

This was a retrospective, population-based study conducted in Alberta, Canada which represents the fourth largest province with a population of over four million residents. The Alberta Cancer Registry (ACR) was the primary data source for patient demographics, tumor characteristics, primary treatment patterns, and survival outcomes, which were collected prospectively for all cancer patients diagnosed in the province. Additional data sources included ambulatory care records, physician billing claims, and hospital discharge abstracts based on previously validated coding algorithms of the International Classification of Diseases (ICD) and Related Health Problems.

2.2. Study population

Patients diagnosed with *de novo* metastatic breast cancer in Alberta from January 1, 2004 to December 31, 2015 were included in the current study. Only those with *de novo* metastatic breast cancer were selected for the current analysis as recurrent events in patients with prior early breast cancer are not recorded in the administrative sources used in this study. Patients who were diagnosed with multiple cancers were excluded. At the outset of the study, it was decided a priori that patients who moved out of the province within one year of diagnosis will be censored at the last date of follow-up for survival analysis. Of note, there were no such patients in our study cohort. Although metastatic breast cancer continues to be an incurable disease, the long-term survival is better than a number of other metastatic cancers (e.g. hepatabiliary, upper gastrointestinal, etc) such that their inclusion would negatively bias the survival outcomes. The study was designed, analysed and reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [19]. The Health Research Ethics Board of Alberta Cancer Committee approved the study prior to its conduct.

2.3. Clinical variables and outcomes

The main outcomes of this study included (i) the receipt of chemotherapy, hormonal therapy and radiotherapy for metastatic breast cancer, and (ii) survival outcomes, including OS and CSS. Items that were considered to be common exclusion criteria in clinical trials were defined in accordance with prior literature [6] and consisted of any of the following: presence of specific comorbid conditions (such as uncontrolled diabetes, cardiovascular, hepatic, or renal disease), abnormal hematologic laboratory parameters, a history of prior cancer and/or immunosuppression within 5 years of their current malignant diagnosis. An upper limit of age was not considered an exclusion criterion as most current clinical trials include patients of all ages.

Individual exclusion criteria were defined as follows: heart disease consisted of complicated hypertension, myocardial infarction or congestive heart failure; liver disease was classified as moderate or severe; abnormal hematological parameters included moderate to severe anemia or coagulopathy; uncontrolled diabetes referred to those with diabetic complications; renal disease was classified as moderate or severe; prior cancer included any malignancy, such as lymphoma or leukemia, except for malignant neoplasms of the skin; immunosuppressive disorders consisted of rheumatoid arthritis, collagen vascular disease, or acquired immunodeficiency syndrome. The ICD codes used for these medical conditions were derived from our previous publication are shown in Supplementary Table 1 [6].

Demographic variables such age, sex, year of diagnosis, and residential postal code were retrieved from the ACR. Postal codes were subsequently used to derive information on neighborhood-level socioeconomic status, including educational attainment and annual household income based on the 2011 census data. The ACR was also used to ascertain binary treatment details (yes/no) pertaining to the receipt of chemotherapy, hormonal therapy, and palliative radiotherapy. The Charlson comorbidity index was generated for each patient using validated algorithms based on physician billing claims and hospital discharge abstracts from the two years preceding the cancer diagnosis [20]. However, data on performance status was not available and therefore it was not included in the analysis.

2.4. Statistical analysis

Descriptive statistics were used to analyse the baseline demographic and treatment-related characteristics. The student's *t*-test and the chi-squared test were used to compare continuous and categorical variables, respectively. Multivariable logistic regression analyses were performed to assess the likelihood of receiving chemotherapy, hormone therapy and radiotherapy. OS was calculated from the date of diagnosis of metastatic breast cancer to the date of death from any cause, censoring at last known follow-up whereas CSS was calculated from the date of diagnosis to the date of death from cancer, censoring at the last known follow-up or death from non-cancer causes. Four subgroups of patients were defined for the outcomes analysis: i) clinical trial eligible patients who received chemotherapy and/or hormone therapy, ii) eligible patients who did not receive any systemic treatment, iii) ineligible

patients who received chemotherapy and/or hormone therapy, and iv) ineligible patients who did not receive any systemic treatment. Radiotherapy was not included as "treatment" because it is not associated with overall survival and it is also administered only for management of symptoms in patients with metastatic breast cancer. Kaplan–Meier curves were used to determine OS and CSS and then log rank tests were used to describe differences across subgroups. To account for the competing causes of death, we also constructed Fine and Grey competing risk models to describe the cumulative incidence functions in different subgroups. Since common exclusion criteria used in this study included comorbid conditions, we tested for multicollinearity between trial-ineligibility and age and Charlson's comorbidity index score by calculating the variance inflation factor (VIF). Based on previous literature, a VIF of less than 10 was interpreted as an absence of multicollinearity [21]. Cox proportional hazards models were constructed to analyse the effect of trial eligibility on survival outcomes, while adjusting for measured confounders. All statistical tests were two-sided, and the significance level was defined a priori as <0.05. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC) and Stata statistical software (StataCorp. 2013. Release 13. College Station, TX).

3. Results

3.1. Patient characteristics

We identified a total of 1585 patients with metastatic breast cancer who were included in the current analysis. The median age at diagnosis was 63 years (interquartile range, 53–75 years). More than one-third of patients were aged over 70 years. Among all patients, 21 (1.3%) were men. While 56.4% of patients had a Charlson comorbidity index of zero, the remainder of patients were evenly distributed across one and more than one. Further, a minority (39.9%) of patients achieved more than high school graduation and a minority (19.1%) had above average annual household income (Table 1).

Overall, 945 (59.6%), 643 (40.6%), and 142(9.0%) received hormonal agents, chemotherapy and radiation treatment, respectively.

3.2. Clinical trial eligibility and treatment

Using common eligibility criteria, 1073 of 1585 (67.7%) patients were classified as eligible and 512 (32.3%) patients were considered ineligible to participate in clinical trials. The most common reason for ineligibility included renal dysfunction (17.2%), followed by previous immunosuppression (7.8%) and cardiovascular disease (7.6%) (Table 2).

Of 1073 eligible patients, 895 (83.4%) were administered systemic treatment, while 380 of 512 (74.2%) trial ineligible received therapy ($P < 0.001$) (Fig. 1). Ineligible patients were less likely to receive chemotherapy (29.5% vs 45.8%; $P < 0.001$) but not radiation therapy (7.6% vs 9.6%; $P = 0.196$) and hormonal therapy (57.6% vs 60.6%; $P = 0.261$).

We compared the characteristics of patients in the four groups: eligible and treated, eligible and untreated, ineligible and treated, and ineligible and untreated. The ineligible and untreated group was comprised of older patients (median age, 77.5 years) and those with a higher Charlson comorbidity index (more than one in 70.5%) as compared with the other three groups. The other characteristics were similar across the four groups (Table 1).

3.3. Factors predicting receipt of chemotherapy, hormonal therapy and radiotherapy

The factors associated with a lower likelihood of administration of chemotherapy included advancing age (odds ratio [OR], 0.93; 95% confidence interval [CI], 0.92 to 0.94; $P < 0.001$), male sex (OR, 0.23; 95% CI, 0.06 to 0.91; $P = 0.040$), and receipt of hormonal therapy (OR, 0.28; 95% CI, 0.22 to 0.37; $P < 0.001$). Conversely, year of diagnosis (OR, 1.06; 95% CI, 1.03 to 1.09; $P < 0.001$), previous surgery (OR, 1.42; 95% CI, 1.05 to 1.93; $P = 0.020$), and previous radiotherapy (OR, 2.14; 95% CI, 1.40 to 3.28; $P < 0.001$) were associated with a higher odd of chemotherapy administration.

A worse Charlson comorbidity index (score more than one, OR, 0.63; 95% CI, 0.45 to 0.87; $P = 0.005$), and prior chemotherapy (OR, 0.29; 95% CI, 0.22 to 0.37; $P < 0.001$) were associated with a lower likelihood of receipt of hormone therapy.

Although administration of radiotherapy was not used to define treatment groups (treated or untreated), we examined the factors associated with its delivery. Previous surgery (OR, 4.29; 95% CI, 0.92 to 0.94; $P < 0.001$) and chemotherapy (OR, 2.09; 95% CI, 1.35 to 3.24; $P < 0.001$) were associated with a higher odd of radiotherapy administration. Of note, trial-eligibility was not related to administration of chemotherapy (OR, 1.36; 95% CI, 0.99 to 1.88; $P = 0.060$), hormone therapy (OR, 1.16; 95% CI, 0.87 to 1.56; $P = 0.310$) and radiotherapy (OR, 0.97; 95% CI, 0.59 to 1.60; $P = 0.910$) (Table 3).

3.4. Survival outcomes

In total, there were 1250 all-cause deaths, of which 1139 (91.1%) were cancer related and 111 (8.9%) were non-cancer related (Fig. 2A). There were 639/895 (71.4%), 171/178 (96.1%), 311/380 (81.8%) and 129/132 (97.7%) deaths in eligible and treated, eligible and untreated, ineligible and treated, and ineligible and untreated patients ($P < 0.001$). The distribution of cancer and non-cancer deaths was similar across the four groups ($P = 0.143$) (Supplementary Table 2). The median OS of eligible and treated patients was 35.4 (95% CI, 32.0–39.9) months compared with 1.9 (95% CI, 1.6–2.5) months in eligible and untreated, 24.7 months (95% CI, 20.0–27.0) months in ineligible patients who received treatment and 2.0 (95% CI, 1.7–2.5) months in ineligible patients who did not receive any therapy (Fig. 2B).

Likewise, the median CSS of eligible and treated patients (39.4 [95% CI, 34.8–43.2 months]) was longer than those who were eligible and untreated (2.2 [95% CI, 1.6–3.0] months), ineligible and treated (25.6 [95% CI, 23.1–30.9 months]), and individuals who were ineligible and did not receive any treatment (2.1 [95% CI, 1.7–2.5 months]), respectively (Fig. 2C).

For CSS, we also calculated the cumulative incidence functions using the Fine and Grey competing risk model. With eligible and treated group as the reference, ineligible and treated patients (subdistribution hazard ratio [SHR] 1.25; 95% CI, 1.09–1.44; $P = 0.001$) had a modestly higher risk of dying due to cancer, while eligible and untreated patients (SHR, 4.22; 95% CI, 3.22–5.52; $P < 0.001$) and those who were ineligible and untreated (SHR, 3.90; 95% CI, 2.82–5.42; $P < 0.001$) had a substantially higher risk of dying due to cancer (Fig. 1D).

3.5. Subgroup analysis

We conducted another analysis restricting the patient cohort to those who did not receive hormone therapy to determine the effect of ineligibility solely on receipt of chemotherapy. There were 640 patients who did not receive hormone therapy. Of these, 217/640 (33.9%) were ineligible and these patients were less likely to receive chemotherapy (39.2% vs 57.9%; $P < 0.001$). The median OS of

Table 1
Baseline characteristics of patients with metastatic breast cancer.

Variable	Total (n = 1585)	Eligible and treated (n = 895)	Eligible and untreated (n = 178)	Ineligible and treated (n = 380)	Ineligible and untreated (n = 132)	P-value
Age, years						
Mean (STD)	63.5 (14.9)	59.5 (13.7)	68.4 (13.5)	66.5 (14.1)	75.8 (12.8)	<0.001
Median (IQR)	63 (53–75)	59 (50–59)	70 (57–80)	68 (56–78)	77.5 (68–88.5)	<0.001
Age group, years						
≤40	98 (6.2%)	74 (8.3%)	7 (3.9%)	15 (3.9%)	2 (1.5%)	<0.001
41–50	217 (13.7%)	151 (16.9%)	16 (9.0%)	47 (12.4%)	3 (2.3%)	
51–60	372 (23.5%)	259 (28.9%)	33 (18.5%)	67 (17.6%)	13 (17.4%)	
61–70	352 (22.2%)	213 (23.8%)	34 (19.1%)	82 (21.6%)	23 (26.5%)	
71–80	304 (19.2%)	130 (14.5%)	44 (24.7%)	95 (25.0%)	35 (26.5%)	
80+	242 (15.3%)	68 (7.6%)	44 (24.7%)	74 (19.5%)	56 (42.4%)	
Year of diagnosis						
2004–2006	256 (16.2%)	150 (16.8%)	25 (14.0%)	61 (16.1%)	20 (15.25)	0.477
2007–2009	303 (19.1%)	158 (17.6%)	42 (23.6%)	76 (20.0%)	27 (20.4%)	
2010–2012	317 (20.0%)	174 (19.4%)	28 (15.7%)	80 (21.0%)	35 (26.7%)	
2013–2015	383 (24.2%)	220 (24.6%)	48 (27.0%)	87 (22.9%)	28 (21.2%)	
2016–2017	326 (20.6%)	193 (21.6%)	35 (19.7%)	76 (20.0%)	22 (16.7%)	
Sex						
Female	1564 (98.7%)	883 (98.7%)	176 (98.9%)	376 (98.9%)	129 (97.7%)	0.758
Male	21 (1.3%)	12 (1.3%)	2 (1.1%)	4 (1.1%)	3 (2.3%)	
CCI score						
0	894 (56.4%)	675 (75.4%)	110 (61.8%)	89 (23.4%)	20 (15.1%)	<0.001
1	355 (22.4%)	184 (20.6%)	53 (29.8%)	99 (26.0%)	19 (14.4%)	
2+	336 (21.2%)	36 (4.0%)	15 (8.4%)	192 (50.5%)	93 (70.5%)	
Chemotherapy						
No	942 (59.4%)	403 (45.0%)	178 (100.0%)	229 (60.3%)	132 (100.0%)	<0.001
Yes	643 (40.6%)	492 (55.0%)	–	151 (39.7%)	–	
Radiation therapy						
No	1443 (91.0%)	793 (88.6%)	178 (100.0%)	341 (89.7%)	132 (100.0%)	<0.001
Yes	142 (9.0%)	103 (11.4%)	–	39 (10.3%)		
Hormone therapy						
No	640 (40.4%)	245 (27.4%)	178 (100.0%)	85 (22.4%)	132 (100.0%)	<0.001
Yes	945 (59.6%)	650 (72.6%)	–	295 (77.6%)	–	
Neighbour's education level, high school or higher attainment						0.566
≤ 80%	950 (59.9%)	519 (58.0%)	111 (62.4%)	241 (63.4%)	79 (59.8%)	
>80%	633 (39.9%)	375 (41.9%)	67 (37.6%)	138 (36.3%)	53 (40.2%)	
Unknown	2 (0.1%)	1 (0.1%)	–	1 (0.3%)	–	
Neighbour's income level, CAD						
≤ 46 k	1281 (80.8%)	712 (79.6%)	144 (80.9%)	314 (82.6%)	111 (84.1%)	0.718
>46 k	302 (19.1%)	182 (20.3%)	34 (19.1%)	65 (17.1%)	21 (15.9%)	
Unknown	2 (0.1%)	1 (0.1%)	–	1 (0.3%)	–	
Health Zone						
Calgary	526 (33.2%)	309 (34.5%)	55 (30.9%)	129 (34.0%)	33 (25.0%)	0.320
Central	235 (14.8%)	125 (14.0%)	27 (15.2%)	65 (17.1%)	18 (13.6%)	
Edmonton	551 (34.8%)	323 (36.1%)	59 (33.2%)	122 (32.1%)	47 (35.6%)	
North	147 (9.3%)	76 (8.5%)	19 (10.7%)	34 (8.9%)	18 (13.6%)	
South	124 (7.8%)	61 (6.8%)	18 (10.1%)	29 (7.6%)	16 (12.1%)	
Unknown	2 (0.1%)	1 (0.1%)	–	1 (0.3%)	–	

STD: Standard deviation; IQR: Interquartile range; CCI: Charlson's comorbidity index.

Table 2
Reasons for ineligibility.

Criteria	Number (%)
Presence of heart disease	120 (7.6%)
Kidney disease	273 (17.2%)
Uncontrolled diabetes	89 (5.6%)
Liver disease	79 (5.0%)
Abnormal bloodwork	53 (3.3%)
Prior malignancy	49 (3.1%)
Previous immunosuppression	124 (7.8%)
Multiple reasons	201 (12.7%)

Note: Some patients met more than one ineligibility criterion and are listed in all the criteria applicable and therefore, the sum of patients in this table is higher than the number of ineligible patients.

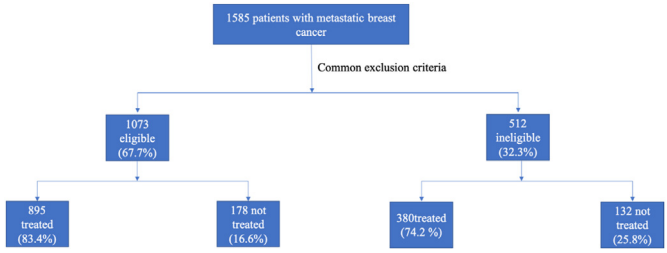

Fig. 1. Flow of patients included in the study.

eligible and treated patients was 24.4 (95% CI, 21.1–27.6) months compared with 1.9 (95% CI, 1.6–2.5) months in eligible and untreated, 21.3 (95% CI, 14.5–29.9) months in ineligible and untreated, and 2.0 (95% CI, 1.7–2.5) months in ineligible and untreated

Table 3
Multivariable logistic regression analysis predicting the likelihood of receiving chemotherapy, hormonal therapy and radiotherapy in patients with metastatic breast cancer.

Variable	Chemotherapy		Hormone therapy		Radiotherapy	
	OR (95% Confidence Limit)	P value	OR (95% Confidence Limit)	P value	OR (95% Confidence Limit)	P value
Age, years	0.93 (0.92–0.94)	<0.001	1.00 (0.99–1.01)	0.995	0.99 (0.98–1.01)	0.335
Year of diagnosis	1.06 (1.03–1.09)	<0.001	1.03 (1.00–1.06)	0.064	0.99 (0.94–1.04)	0.605
Ineligibility						
Ineligible	Reference		Reference		Reference	
Eligible	1.36 (0.99–1.88)	0.057	1.16 (0.87–1.56)	0.308	0.97 (0.59–1.60)	0.909
Sex						
Female	Reference		Reference		Reference	
Male	0.23 (0.06–0.91)	0.036	1.87 (0.62–5.62)	0.265	1.79 (0.47–6.85)	0.394
CCI score						
0	Reference		Reference		Reference	
1	1.04 (0.76–1.42)	0.798	0.77 (0.58–1.01)	0.061	0.82 (0.50–1.35)	0.438
2+	0.70 (0.47–1.04)	0.078	0.63 (0.45–0.87)	0.005	0.92 (0.49–1.71)	0.789
Surgery						
No	Reference		Reference		Reference	
Yes	1.42 (1.05–1.93)	0.023	1.50 (1.13–1.98)	0.005	4.29 (2.76–6.66)	<0.001
Chemotherapy						
No	–	–	Reference		Reference	
Yes	–	–	0.29 (0.22–0.37)	<0.001	2.09 (1.35–3.24)	<0.001
Radiation therapy						
No	Reference		Reference		–	–
Yes	2.14 (1.40–3.28)	<0.001	1.22 (0.83–1.81)	0.313	–	–
Hormone therapy						
No	Reference		–	–	Reference	
Yes	0.28 (0.22–0.37)	<0.001	–	–	1.32 (0.88–1.98)	0.184
Neighbour's education level, high school or higher attainment						
≤ 80%	Reference		Reference		Reference	
>80%	0.83 (0.63–1.11)	0.206	1.1 (0.86–1.42)	0.457	0.81 (0.53–1.25)	0.352
Neighbour's income level, CAD						
≤ 46 k	Reference		Reference		Reference	
>46 k	1.16 (0.83–1.63)	0.378	1.15 (0.85–1.56)	0.369	0.87 (0.50–1.50)	0.606
Zone name						
Calgary	Reference		Reference		Reference	
Central	0.99 (0.66–1.47)	0.951	0.90 (0.63–1.28)	0.560	1.47 (0.78–2.78)	0.235
Edmonton	0.68 (0.51–0.92)	0.012	0.65 (0.50–0.84)	0.001	1.92 (1.19–3.09)	0.007
North	0.65 (0.41–1.03)	0.069	0.77 (0.51–1.17)	0.217	1.63 (0.81–3.30)	0.171
South	0.76 (0.46–1.28)	0.306	0.84 (0.54–1.31)	0.439	1.95 (0.90–4.20)	0.089

OR: Odds ratio; CCI: Charlson's comorbidity index.

patients (Supplementary Table 3).

3.6. Cox regression models for OS and CSS

We constructed multivariable Cox regression models to assess the impact of eligibility on OS and CSS, while accounting for measured confounders. There was no multicollinearity between trial-ineligibility and age (VIF = 1.3) or the Charlson's comorbidity index (VIF = 1.3).

As compared to ineligible patients, there was no difference in OS in eligible patients (hazard ratio [HR], 0.90; 95% CI, 0.78 to 1.04; P = 0.168) after adjusting for treatment. Receipt of chemotherapy (HR, 0.44; 95% CI, 0.38 to 0.51; P < 0.001) or hormonal therapy (HR, 0.30; 95% CI, 0.26 to 0.34; P < 0.001) were associated with better OS. Factors that predicted worse OS included advancing age (HR, 1.02; 95% CI, 1.01 to 1.02; P < 0.001). Socio-economic status (income [P = 0.626] and education levels [P = 0.143]), sex (P = 0.458), Charlson comorbidity index (P = 0.975 for score of one and P = 0.202 for score of more than one, with reference score of zero), and receipt of radiation treatment (P = 0.414) did not impact on OS (Table 4).

Likewise, the CSS of eligible patients and those deemed ineligible were similar (HR, 0.89; 95% CI, 0.76 to 1.04; P = 0.160). Receipt of chemotherapy (HR, 0.44; 0.38 to 0.51; P < 0.001) or hormonal therapy (HR, 0.29; 0.25 to 0.33; P < 0.001) were predictive of longer CSS. Conversely, advanced age predicted worse CSS (HR, 1.01; 95% CI, 1.01 to 1.02; P < 0.001). Notably, there were no associations of receipt of radiation treatment (P = 0.187), Charlson comorbidity index (P = 0.884 for score of one and P = 0.676 for score of more than one, with reference score of zero), sex (P = 0.407), and socioeconomic status (P = 0.501 for income and P = 0.209 for education) with CSS.

4. Discussion

In this study, we found that one-third of real-world patients with metastatic breast cancer were ineligible to participate in clinical trials based on common eligibility criteria. The most common reason for ineligibility was coexisting renal dysfunction. However, approximately one-fourth of ineligible patients still received chemotherapy and over half still received hormonal therapy in the real-world setting. Of note, ineligible patients who received systemic therapy experienced a median OS of two years as compared to two months in those who did not receive any treatment. Eligibility for clinical trials was not associated with CSS as well as OS, after accounting for other confounding factors.

While previous studies have reported that the rate of ineligibility in various cancers can be as high as 80%, a potential driver for the wide variability could be the inclusion of a heterogenous group of cancers in most of the prior research [6] [–] [8]. To that end, this is one of the first studies to include patients with metastatic breast cancer exclusively. A survey study of physicians demonstrated that 39% of breast cancer patients were offered to participate in ongoing clinical trials, but only 12% were ultimately enrolled [22]. The study

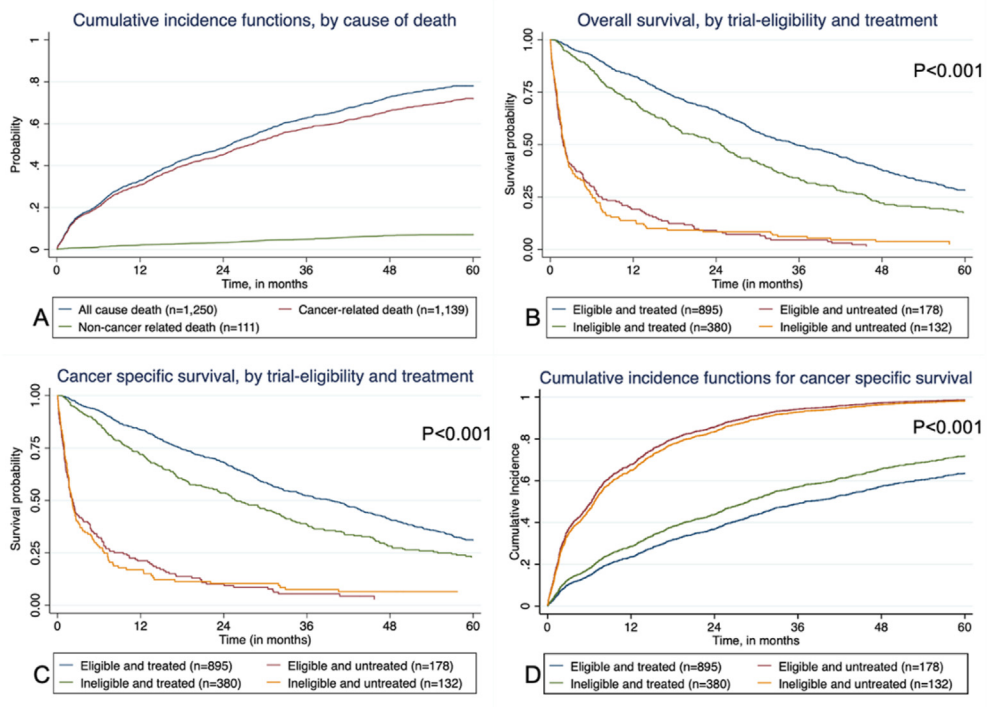

Fig. 2. Distribution of causes of death (A); overall survival (B), cancer-specific survival (C), and cumulative incidence functions of cancer-specific survival (D) of patients with metastatic breast cancer by clinical trial eligibility and treatment (eligible and treated, eligible and untreated, ineligible and treated, and ineligible and untreated).

Table 4
Multivariable Cox regression model for overall survival and cancer-specific survival in patients with metastatic breast cancer.

Variable	Overall survival		Cancer-specific survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	1.02 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	<0.001
Year of diagnosis	0.99 (0.94–1.03)	0.563	0.95 (0.91–0.99)	0.047
Ineligibility				
Ineligible	Reference		Reference	
Eligible	0.90 (0.78–1.04)	0.168	0.89 (0.76–1.04)	0.160
Sex				
Female	Reference		Reference	
Male	1.20 (0.74–1.94)	0.458	1.23 (0.75–2.03)	0.407
CCI score				
0	Reference		Reference	
1	1.00 (0.86–1.15)	0.975	0.99 (0.85–1.15)	0.884
2+	1.13 (0.94–1.35)	0.202	1.04 (0.86–1.27)	0.676
Chemotherapy				
No	Reference		Reference	
Yes	0.44 (0.38–0.51)	<0.001	0.44 (0.38–0.51)	<0.001
Radiation therapy				
No	Reference		Reference	
Yes	0.92 (0.75–1.12)	0.414	0.87 (0.70–1.07)	0.187
Hormone therapy				
No	Reference		Reference	
Yes	0.30 (0.26–0.34)	<0.001	0.29 (0.25–0.33)	<0.001
Neighbour's education level, high school or higher attainment				
≤ 80%	Reference		Reference	
>80%	0.91 (0.80–1.03)	0.143	0.92 (0.80–1.05)	0.209
Neighbour's income level, CAD				
≤ 46 k	Reference		Reference	
>46 k	0.96 (0.82–1.13)	0.626	0.94 (0.79–1.12)	0.501
Health zone				
Calgary	Reference		Reference	
Central	1.00 (0.83–1.20)	0.986	1.03 (0.85–1.24)	0.753
Edmonton	1.11 (0.96–1.27)	0.155	1.13 (0.98–1.31)	0.104
North	0.98 (0.79–1.21)	0.841	0.95 (0.76–1.20)	0.679
South	1.32 (1.05–1.65)	0.015	1.35 (1.07–1.70)	0.011

HR: Hazard ratio; CI: Confidence interval; CCI: Charlson's comorbidity index.

included patients with all stages of breast cancer and 26% of included patients had metastatic breast cancer. While non-availability of a suitable trial was reported as the primary reason (53%) for not offering study participation to patients, ineligibility was the second most common cause (47%). Second-opinion consultations and ongoing treatments were noted as additional reasons for ineligibility. A remarkable observation is that the ineligibility rates are strikingly similar between the older study and the current study, despite an interval of more than 25 years between studies. Despite innovations in clinical trial designs and advances in statistical methods, our observation suggests that little progress has been made to improve the representativeness of clinical trial participants over the past two decades.

Advancing age and comorbid conditions have been the most frequently cited reasons for rendering patients ineligible to participate in clinical trials [6] [–] [8]. Most current clinical trials do not consider an upper age limit to participate in clinical trials and therefore, we did not apply it as an exclusion criterion. If age more than 75 years was also applied as an additional exclusion criterion in our study, the number of ineligible patients increased from 512 (32.3%) to 693 (43.7%). The burden of comorbid conditions increases with advanced age. This observation is counterintuitive since the median age of diagnosis of breast cancer is 62 years, and approximately one-fifth of those diagnosed are aged more than 75 years [23]. In a large population-based study, 64.9% of people aged 65–84 years, and 81.5% of people aged 85 years or older, were reported to have at least 2 chronic conditions [24]. With the changing demographics of an aging population, it is anticipated that an increasing number of real-world patients will be older and have more significant and complex comorbidity burdens, underscoring a pressing need to make clinical trial criteria more pragmatic and reflective of patients in whom the drugs will actually be used.

We found that trial-eligibility did not predict for the administration of chemotherapy, hormone therapy, and radiotherapy. This

finding suggests that the criteria used for treatment decision making in the real world are discordant from those used for screening in clinical trials. To this end, the American Society of Clinical Oncology and Friends of Cancer Research have recently released a joint research statement to underscore the need for trial enrollment criteria to strive for inclusiveness. Ideally, entry criteria should be liberal with respect to age, organ function, and prior and concurrent malignancies [25]. Factors associated with no systemic treatment included advancing age and high comorbidity burden. Further, around one-sixth of ineligible patients did not receive any systemic therapy and this likely reflects non-treatment secondary to patients' own preferences.

Future trials must therefore broaden the eligibility criteria so that an unselected patient population is provided an opportunity to participate. Chronological age is a poor surrogate marker of physical frailty and functional status in older adults [26]. A comprehensive geriatric assessment has previously been validated in patients with cancer to assist in decision making and to predict complications and adverse events from chemotherapy [27] [–] [30]. It may be reasonable to consider a comprehensive geriatric assessment rather than chronological age as an eligibility criteria for clinical trials. Likewise, the presence of a comorbid condition by itself as an exclusion criterion is a barrier for many patients and therefore consideration of a comorbidity's severity is likely to better correlate with treatment tolerance. By adopting an approach that accounts for some of the nuances and inter-patient differences, we hypothesize that clinical trial findings would have more relevance to the population of interest.

The study was limited by its retrospective design. The data were collected from administrative sources and therefore important clinical parameters such as performance status and disease progression events were not available to a reliable degree. In addition, the exclusion criteria that were used in our analyses were derived empirically from elements common to most studies rather than from individual trials of metastatic breast cancer since there are trial-to-trial differences based on the drug and setting. Therefore, patients deemed ineligible in our study may still be eligible for specific clinical trials, and vice-versa. Our study population in the current analysis comprised of *de novo* metastatic breast cancer, while most patients with metastatic breast cancer present with a recurrence from a prior diagnosis of early stage breast cancer. Patients with *de novo* breast cancer are likely to be older, have hormone receptor positive breast cancer, and experience longer OS as compared with those presenting with recurrent metastatic breast cancer due to their therapy-naïve status or lower resistance to systemic treatment [31,32]. Further, a prospective study would be needed in order to understand preferences of eligible patients and why some of these individuals would decline to actually participate in clinical trials. This was beyond the scope of the current analysis. Lastly, the exact causes of death of patients who died of non-cancer related deaths were not known. All of these limitations should be weighed against its strengths, one of which is its large population-based design and its representation of all patients with metastatic breast cancer in the province.

5. Conclusion

In conclusion, patients with metastatic breast cancer in the real world who are not eligible for participation in clinical trials appear to still derive potential benefit from systemic treatment in the real world. Our findings support broadening the eligibility criteria in clinical trials to increase representativeness and generalizability. Bridging the gap between internal validity of clinical trials and external validity of real-world evidence will become increasingly important as the population ages and faces a growing comorbidity burden, and will better inform care in the real world.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.10.005.

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Data statement

The data can be shared with the journal for review, if needed.

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