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They Need Extra Care Now: Using Potentially Inappropriate Medicine in Metastasis Breast Cancer by Older Adults in Iraq and Aftermaths

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Abstract

Background: Elderly patients frequently use multiple medications since they are more likely to have multiple ailments. Therefore, potentially inappropriate medication (PIM) use affects older breast cancer patients' overall physical and mental health. Caretakers must therefore exercise caution in such circumstances.

Aim: This study's primary goal is to identify the potentially inappropriate medications (PIMs) given to older Iraqi patients with metastatic breast cancer.

Methodology: The Medicare claims-related "Surveillance, Epidemiology, and End Results" (SEER) database was used for this investigation. Patients with metastatic breast cancer who were 66 years of age or older were included in this cohort research. Between 2017 and 2019, they received a stage III or stage II breast cancer diagnosis. The "Beers criteria" and the "Drugs to Avoid in the Elderly" (DAE) list were used to determine the PIM use for this study. This study also carried out multivariate and univariate analysis about PIM usage. "event-free survival" was defined as the time from the start of chemotherapy to the occurrence of an event (emergency department visit, death, hospitalization, or a composite). The "Cox proportional hazards" model was employed to ascertain the association between EF and PIM usage.

Results: 1495 patients with metastatic breast cancer were chosen for analysis. Baseline PIM was observed to occur 26.7% of the time in the DAE list and 30.23% in the context of Beers criteria. Additionally, it was noted that approximately 44% of breast cancer patients experienced at least two negative outcomes. Except for overall survival in the DAE list, the time-to-event analysis found no correlation between baseline PIM use and other products.

Conclusion: The findings of this study indicated that older breast cancer patients were more likely to experience negative outcomes due to polypharmacy. Therefore, healthcare professionals need to be especially cautious regarding PIMs.

Keywords:

Potentially Inappropriate Medicine; Metastasis Breast Cancer; Iraq; Cohort; Polypahrmacy

Introduction

Potentially inappropriate medications are classified as having a higher risk for older people relative to the advantages they provide and should be avoided by older people (PIM).[1] The Beers criteria, created to gauge PIMs, are a well-known and frequently applied construct.[2] The Beers criteria were updated to cover extremely dangerous drugs to protect older patients' health and prevent drug interactions.[2] The instrument's usefulness has been constrained despite the introduction of

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the Beers criterion. The tool's applicability has been hampered by the absence of the drugs included in the requirements in nations other than the United States. PIM use is widespread among elderly cancer patients.[3, 4] PIM use has increased the likelihood of unfavorable outcomes for elderly cancer patients during their cancer treatment.[5, 6] Because cancer patients are prescribed various medications to address their disease, cancer, and therapy-induced toxicity, PIM is thought to be a risk factor for older cancer patients.[7] Elderly oncology patients seeing multiple doctors for their therapy, which may lead to receiving drugs for related symptoms, is another factor that raises the risk.[8] Older cancer patients need various therapy due to comorbidities. A serious health problem is a polypharmacy, which involves the simultaneous use of five or more medications.[8] As a result, older cancer patients are also more likely to experience polypharmacy, which leads to using PIMs.[9] Many oncology departments follow recommendations that drugs for elderly cancer patients should be checked with screening tools at every visit to ensure proper therapy.[6] Due to their altered physiology, patients with cancer are hypersensitive to medications; as a result, a comprehensive assessment of medications is necessary to guarantee safe administration.[10, 11] Additionally, studies show that patients with metastatic cancer are more likely to continue taking their prescriptions to avoid comorbidities.[12] The usage of PIM has a detrimental effect on older people's health. Due to the negative effects of use, there is a rise in emergency room visits and hospitalizations and a higher risk of mortality.[1, 13] Furthermore, chemotherapy side effects are more likely to affect elderly cancer patients.[6] The use of PIM reduces the effectiveness of chemotherapy and increases chemotherapy-related damage.[14] A study conducted in Turkey found that drug-to-drug interactions were common in one-third of elderly cancer patients who used PIMs.[15] However, the number of hospitalizations, increased toxicity, and comorbidities, among other outcomes of using PIMS, remained unclear in a few trials.[14]

Breast cancer is the most common cancer in women and the main reason women die from cancer globally.[16]

In 2020, more than 2 million female breast cancer diagnoses will likely occur. 6.9% of all female cancer-related fatalities were attributable to breast cancer.[16] Research in Iraq has shown that women over 70 are most at risk for breast cancer, which is more common in older women.[17, 18] From 2000 to 2019, there were more breast cancer cases reported in Iraq.[16] There is little data on PIM use among elderly cancer patients in Iraq who have metastasized. As a result, a thorough study is required to evaluate PIM use among older women in Iraq who have breast cancer.

The current study aims to advance knowledge by analyzing the effects of PIM use on the health of older Iraqi patients with metastatic breast cancer. The current research seeks to identify patient and disease characteristics in older breast cancer patients with metastatic illness following baseline PIM usage and (ii) examine the impact of baseline PIM use on the health outcomes of older breast cancer patients with adjuvant chemotherapy.

The literature is reviewed in Chapter 2 of the book. In Chapter 3, the research technique is covered before the conclusions. The study's conclusions offer useful insights and suggestions for the future once it has discussed its findings.

Literature Review

Potentially Inappropriate Medicine (PIM)

According to research, several medications may not be recommended for patients 65 years or older. Prescriptions for these potentially inappropriate medications (PIM) should not be made for elderly patients. The primary factor, in this case, is that these medications affect people differently depending on their age.[19] When treating elderly adults, polypharmacy and multimorbidity are the main problems. They use a variety of medications for various illnesses. Due to age-related changes in pharmacokinetics and -dynamics, the first-pass effect manifests in the liver, and renal function and elimination are slower in elderly individuals. Because senior people's bodies retain medications longer than those of younger ones, this leads to different pharmacological effects in them. There is insufficient information on this subject because studies on how specific medications affect older people have not been conducted individually.[20, 21] According to studies, many elderly patients have been hospitalized in hospitals due to adverse drug reactions or because they combined two medications. Due to this problem, PIM (drugs that may be dangerous for older people) blocklists have been created by governments.[22]

Due to diverse marketplaces, different countries have varied PIM listings. These lists include medications with higher risks than benefits, a higher chance of intolerance, and a higher likelihood of adverse events. These lists contain some recommendations for supervision if there is no alternative for such medications. These medications are administered despite their risks and dangers for several reasons. The effects of PIM and their awareness by physicians are insufficient. As a result, they prescribe them based only on their own opinions and without sufficient proof. Additionally, they frequently lack time and engagement with other medical professionals. These doctors do not locate any alternatives for these medications because they are unsure about the issue. Additionally, they believe it is difficult to interpret such PIM lists. The patients themselves, on the other hand, take a lot of medications despite having little knowledge about them. Patients occasionally see multiple doctors at once, which might cause an issue because they do not tell any of them about the other visits. Therefore, all of these parameters have a role in recommending PIM

medications. According to research, patients' preferences for various medicines and their consultations about such drugs may also impact PIM prescriptions. The decision to prescribe PIM may also be influenced by the doctor's knowledge of medications and how those medications affect other patients.[19, 23]

Potentially Inappropriate Medicine in Metastasis Breast Cancer

Older adults with cancer typically take multiple medications due to various medical issues. Therefore, serious drug interactions (SDIs) are common in cancer patients due to PP. Several medications and SDIs may have unwanted side effects, including increased fall risk, weakness, adverse events (AEs), and decreased effectiveness of several chemotherapy therapies.[24, 25] According to research, using PIM medications increases chemotherapy's toxicity and prolongs hospital stays. It has been discovered that using PIM medications in cancer patients is also associated with subpar performance, tumors, and readmission to the hospital. However, some studies support the opposite.[15, 26] According to studies, people with cancer need to take extra precautions because their situation is more complicated than others'. Additionally, they recommend that medical professionals receive specialized training and education on dealing with cancer patients. They ought to be aware of the worsening consequences on cancer patients.[27] Additionally, a recent study reveals that PIM users are more likely to die and need more ER care. Age and being a man both raised the likelihood of dying; those 65 and older had a twofold higher risk of dying compared to the youngest age group. Having at least three persistent conditions, having advanced cancer, and using more chemotherapy drugs were additional characteristics that were substantially connected to a higher chance of mortality. Cancers of the lungs, bronchi, female genitalia, or digestive system had the highest mortality rates, whereas breast and prostate cancer had the lowest mortality rates.[15, 28] These studies do, however, have some restrictions. For instance, no research has been done on breast cancer metastasis. Furthermore, these investigations do not cover several cancer types that demand attention.

3. Methodology

Study design

Cohort studies entail tracking study participants throughout time (often many years). Cohort studies specifically include and track comparable issues, such as a particular occupation or racial similarity. Throughout the follow-up period, some cohort members may experience a specific potential risk or feature; the impact of this parameter can be studied by tracking findings over time. Thus, cohort studies are crucial in epidemiology because they assist in identifying the factors that increase or decrease the risk of contracting a disease. A study of the retrospective cohort was done using the SEER-Medicare linked dataset.[29] The index date, designated as the day of the occurrence, saw the discovery of the primary (breast cancer) malignancies. The period spanning was set as one year before the index date. The evaluation time for calculating the major independent factor was established as one year from the index date (PIM use). The dependent variables—including the frequency of ER visits, inpatient consultations, and hospital expenses—were assessed after the evaluation period. We chose the durations of the diagnostic and follow-up procedures to comprehend better the significant financial burden of a cancer diagnosis and the ensuing therapy.

Data Source

The combined Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset served as the data source. The population-based tumor registry, known as SEER, is sponsored by the National Cancer Institute and contains information on all newly discovered cancer cases that impact residents of participant areas. The Medicare claims data linked to SEER includes information on doctor claims, inpatient claims, and outpatient claims. Part D Prescription Medicine Events records, including details about the prescription medications, fill date, National Drug Code number, volume distributed, several days' supplies, price, and other plan-specific elements have been linked using beneficiaries' identities from Medicare claims records.[30]

Study Population

The study comprised 1495 patients with adjuvant chemotherapy who were 66 years of age or older and had been diagnosed with breast cancer. For those who had been recognized, Medicare Part A and B coverage for at least 12 months before and after a diagnosis and Part D coverage for 4 to 12 months were required. Participants who were a part of a health maintenance department at any time throughout the year before and after their diagnosis were not included due to false statements. Male breast cancer was not accepted.

Measures

To estimate the prevalence of adjuvant chemotherapy, we looked at the SEER-Medicare Outpatient, Physician/Supplier, and Durable Medical Equipment files. To qualify as an adjuvant chemotherapy claim, the treatment must begin within six months after the diagnosis. After the last J codes for chemotherapy showed, the patient's active treatment ended. There was no further medication administered for at least 90 days. Plans for treating breast cancer that included the J codes for doxorubicin, epirubicin, or mitoxantrone were classified as anthracycline-based. Concomitant diseases prevalent during the year before the cancer diagnosis were discovered utilizing the International Classification of Conditions, Ninth Revision, diagnostic and treatment coding, and Medicare inpatient, outpatient, and physician claim data. Using a macro provided by the National Cancer Institute, the Charlson Comorbidity Index, modified by Charlson *et al*.[31], was used to calculate the comorbidity score. Using statistical tract-level education

and socioeconomic data, we determined the proportion of patients with less than 12 years of schooling, including those who were extremely poor.

Statistical Analysis

The main objective was to determine how common initial PIM use and associated characteristics were in older adult breast cancer patients receiving adjuvant chemotherapy. PIM usage was established using the 2012 Beers criterion and the DAE list.[32] Both tools have been used retroactively on a combined set of records. Pharmaceuticals were counted if patients received a single prescription for a supply lasting at least 90 days or a 30-day supply with more than one refill. PIM usage was quantified for each tool using a dichotomous scale (present or absent). Additionally, PIM rates from 0 to 3 months and 3 to 6 months after the initiation of treatment were evaluated. For each cohort, PIM frequencies and other baseline sample data were calculated using descriptive statistics. Univariate and multivariate logistic regression were carried out to examine the link between study variables and each PIM consumption parameter. Cox proportional hazards models were fitted to investigate the association between patient and clinical characteristics and time-to-outcome endpoints, and the central predictive hypothesis was evaluated (PIM use). The components in the final model were chosen based on their clinical and statistical applicability. The results were presented using hazard ratios and 95% confidence intervals. With SAS 9.3, all statistical analysis was completed (SAS Institute, Cary, North Carolina).

Results

Results for the current study are presented in this section, with an emphasis on baseline PIM use frequency, clinical patient characteristics, time-to-event analysis, and the CPH model for patients with metastatic breast cancer.

Characteristics of Patients

Table 1 lists the characteristics of the 1495 people chosen for the study, showing that 82.6% were Arabs, 10.7% were black Iraqis, and 6.68% were of other races. The chosen people were also distributed according to their diagnosis years, which ranged from 2017 to 2019. Only 8.16% of the randomly chosen breast cancer patients were over 80, making up around 47.49% of the patient population. Cancer stage, CCI, number of drugs, and number of healthcare providers were among the traits of other patients. 73.24% of the patients received non-anthracycline-based therapy, compared to 26.75% of patients who received anthracycline-based treatment.

Table 1: Characteristics of patients

Characteristics	Metastasis breast cancer Cohort (N=1495)	(%)
Arabs	1235	82.6
Black Iraqis	160	10.7
Others	100	6.68
First diagnosis year		
2017	305	20.4
2018	610	40.8
2019	580	38.79
Diagnosis age (years)		
66 to 70	710	47.49
71 to 75	450	30.10
76 to 80	213	14.24
More than 80	122	8.16
Stages		
Stage II	1150	76.9
Stage III	345	23.07
CCI		
0	900	60.20
1	400	26.75
≥ 2	195	13.04
No. of DM at baseline		
0 to 4	400	26.75
5 to 10	645	43.14
> 11	450	30.10
No. of CP at baseline		
0 or 1	615	41.1
2 or 3	700	46.8
≥ 4	180	12.04
A chemotherapy regimen (metastasis breast cancer)		
Anthracycline	400	26.75
Non-anthracycline	1095	73.24

CCI=Charison Combordity Index; CP=care providers; DM=different medications

Frequency of PIM Use

Table 2 shows that the PIM use ranged from 12% to 32% in all timeframes for the bees criteria and DAE list except for ≥ 3 to 6 months in the DAE list, where its value is 6.3%. However, in all cases, the PIM use was low in the≥ 3 to 6 months timeframe.

Table 2: Frequency of PIM use during different timeframes

Measures	Timeframe	Breast cancer Cohort (n/N)	(%)
DAE	Baseline	400/1495	26.7
	Before chemotherapy	520/1495	34.7
	0 to ≤ 3 months	480/1495	32.1
	≥ 3 to 6 months	95/1495	6.3
Beers	Baseline	452/1495	30.23
	Before chemotherapy	490/1495	32.7
	0 to ≤ 3 months	360/1495	24.08
	≥ 3 to 6 months	193/1495	12.9

DAE=Drugs to avoid in elderly

Clinical Characteristics of Patients

The multivariate and univariate analysis results in the context of baseline PIM use are presented in table 3. For metastasis breast cancer cohort in the context of multivariate analysis, both Beers and DAE criteria have a baseline PIM use associated with younger age and ≥ 5 medications.

Table 3: Clinical characteristics of patients following baseline PIM use

Characteristics	Metastasis Breast Cancer Cohort, odd ratio (95% CI), p-value	
DAE	**Univariate**	**Multivariate**
Diagnosis Age (years)		
66 to 70	Ref.	Ref.
71 to 75	0.88 (0.67-1.16), .4100	0.82 (0.61-1.12), .2200
76 to 80	0.87 (0.61-1.23), .4500	0.78 (0.54-1.13), .2200
More than 80	0.55 (0.36-0.90), .2100	0.45 (0.26-0.73), .0011
CCI		
0	Ref.	
1	1.3 (1.06-1.83), .0141	
≥ 2	1.72 (1.22-2.37), .0011	
No. of DM		
0 to 4	Ref.	Ref.
5 to 10	2.98 (1.98-4.6),<.00011	3.12 (2.08-4.72),<.00011
> 11	7.23 (4.83-10.83),<.00011	7.66 (5.10-11.4),<.00011
No. of CP		
0 or 1	Ref.	
2 or 3	1.34 (1.03-1.75), .0231	
≥ 4	1.84 (1.2-2.61), .00061	
Beers		
Race		
Arabs	Ref.	
Black Iraqis	0.93 (0.61-1.43)	
Others	0.99 (0.62-1.62)	
CCI		
0	Ref.	
1	1.70 (1.32-2.20),<.00011	
≥ 2	2.57 (1.8-3.4),<.00011	
No. of DM		
0 to 4	Ref.	Ref.
5 to 10	3.43 (2.35-5.02), .00011	3.43 (2.35-5.02),<.00011
> 11	8.44 (5.7-12.32), .00011	8.44 (5.7-12.32),<.00011
No. of CP		
0 or 1	Ref.	
2 or 3	1.53 (1.21-2.95), 0.00061	
≥ 4	1.88 (1.34-1.54), .0021	

CCI=Charison Combordity Index; CP=care providers; DM=different medications; Ref.=Reference; CI=confidence interval; DAE=Drugs to avoid in elderly

Time-to-event Analysis

The "time-to-event analysis" for metastatic breast cancer is presented in Table 4. This table shows roughly 36.2% of emergency room visits, 24.4% of hospital stays, 1.6% of fatalities, and 38.12% of composite events. The median follow-up was 5.6 months, with a follow-up range of 0 to 9 months. In one year, EFR values for ER visits were 48%, hospital stays were 61%, fatalities were 95%, and composite events were 44%. A link between older age and emergency department visits was also revealed by multivariate analysis, while hospital trips are more common among black Iraqis.

Table 4: Period summary from 1st chemotherapy to an event for metastasis breast cancer

	ER (n, %)	Hosp.	Death	ER/Hosp./Death
Events	542 (36.2)	359 (24)	24 (1.6)	570 (38.12)
F-U, (med), (mo)	5.1	5.2	5.6	5.1
F-U, (ran.), (mo)	0 to 9	0 to 9	0 to 9	0 to 9
1-year EFR	0.48 (0.45-0.51)	0.61 (0.58-0.64)	0.95 (0.93-0.98)	0.44 (0.41-0.47)

F-U=follow-up; mo=month; med=median; ran.=range; ER=emergency room; Hosp.=hospitalization; EFR=event-free rate

CPH Model

Table 5 displays the "Cox proportional hazards" model. The findings revealed that, for all cases in the context of DAE and Beers criteria, the value of p was less than 0.05, except for the overall survival in the context of "time-to-event analysis." In the DAE list, the value of p was discovered to be.032 for overall survival. Thus, it demonstrates that there is a relationship between baseline PIM use and overall survival in the context of the DAE list. However, a correlation between baseline PIM use and any other criterion or cases is not seen.

Table 5: CPH model

PIM measures	1st ER, hazard ratio (95% CI), p-value	1st hosp., hazard ratio (95% CI), p-value	OS, hazard ratio (95% CI), p-value	1st hosp./ER/death, hazard ratio (95% CI), p-value
DAE	0.95 (0.77-1.17), .6700	0.95 (0.74-1.22), .7310	2.32 (1.06-4.97), .032	0.95 (0.78-1.16), .6810
Beers	1.03 (0.84-1.23), .8320	1.0 (0.78-1.25), 1.0001	1.85 (0.87-3.95), .1110	0.98 (0.81-1.18), .9210

ER=emergency room; Hosp.=hospitalization; CI=confidence interval; CPH=Cox Proportional Hazards

Discussion

The current investigation aimed to identify baseline PIM consumption among older patients with metastatic breast cancer to identify patient and illness features. Additionally, it looked at the effects of baseline PIM use on older breast cancer patients' chemotherapeutic outcomes on their health. The statistics indicate a substantial usage of PIM medications among elderly cancer patients. In all timeframes for the Bees criteria and DAE list, the PIM use varied from 12 to 32%, according to the data, except for the ≥3 to the 6-month timeframe for the Beers criteria, where its value is 6.3%. The findings are consistent with Saarelainen's earlier research.[25, 33] It implies that elderly cancer patients use PIM to manage various medical issues, even undergoing chemotherapy. Older individuals frequently have multiple health issues, which can cause polypharmacy and dangerous drug interactions. As a result, individuals may experience negative drug interactions and side effects.[14] The study's findings support the association. It explains how older metastatic breast cancer patients' use of PIM and polypharmacy due to multimorbidity while undergoing chemotherapy negatively impact their health. They experience more responses and negative effects while taking multiple PIM medications for cancer therapy than when taking multiple PIM drugs for other conditions. Additionally, chemotherapy can intensify the negative impact of the various medications' reactions. These older cancer patients may require hospitalization more frequently than other patients without cancer, according to the significance of the examined variables. Additionally, chemotherapy weakens and exposes them, increasing their susceptibility to adverse effects. They are more likely to pass away from polypharmacy and PIM during chemotherapy. These patients go to the emergency room more often than other patients. These results are consistent with those of a prior study by Tamara Dean in 2021.[28] The study also discovered the negative effects of polypharmacy and PIM in the form of frequent readmissions to hospitals, increased ER visits, and higher death rates resulting from such reactions in cancer patients. Contrary to Tamara's report, this one explains that metastatic breast cancer survivors still experience a greater rate of death, more hospitalizations, and more ER visits even after chemotherapy. Even when cancer treatment is over, chemotherapy and polypharmacy from PIM use make individuals more weak and susceptible to responses that have negative effects. They have also often visited hospitals and emergency rooms after receiving cancer treatments. Even after overcoming cancer therapies, they have a higher mortality rate than other patients. It suggests that to lessen the negative effects of polypharmacy and PIM use, such individuals need special attention and vigilance. Medical professionals need to be aware of how various drugs affect cancer patients. They will be better able to comprehend the issue thanks to this study and treat patients with metastatic breast cancer accordingly.

Conclusion

Our study aimed to evaluate the effects of PIM use on the health of older women in Iraq who had metastatic cancer. To identify the illness characteristics of baseline PIM use and to assess the impact of baseline PIM on the health outcomes of these patients after adjuvant chemotherapy, the study used data from 1,495 metastatic breast cancer patients. The use of PIM by older Iraqi women is widespread. The study's results showed that baseline PIM use during adjuvant chemotherapy negatively impacts the health of older Iraqi women with metastatic breast cancer. Additionally, composite occurrences of emergency, hospitalization and deaths were significantly more frequent than both emergency and hospitalization visits. The present study will help oncologists, doctors, and other oncology practitioners become more aware of the disease. It can help them understand the cumulative effects of taking various medications during and after chemotherapy for patients with metastatic breast cancer. Due to the complexity of these patients, doctors must have more education and training in this area. This study will add to the body of knowledge on metastatic breast cancer and help to find a cure.

Unlike earlier studies, this one particularly examined the link between breast cancer and age, providing a clearer picture of older breast cancer patients. PIM may affect cancer in many ways, but this information is hard to come by because so little research has focused on specific cancer types.

In conclusion, the present study's results will benefit patients and physicians who treat metastatic breast cancer. The patients will more likely experience an improved quality of life and better physical and mental health because the doctors will be better prepared with the necessary knowledge to tailor treatments with safer and more suitable combinations of medications and chemotherapy to deliver better health outcomes.

Practical implications

The current study has contributed to the knowledge of PIM use among older women in Iraq who had metastatic cancer. The study has practical consequences in addition to theoretical ones because it makes oncologists and other doctors more aware of baseline PIM use, Beer's criteria, and DAE criteria. Doctors should review the medication and prescription histories of older women with metastatic breast cancer. The findings can be used by health authorities and regulatory agencies to firmly implement the monitoring and reviewing of prescriptions for medications for older women with breast cancer in Iraq.

Limitations and future research recommendations

The study has shortcomings despite its insightful findings. The findings cannot be applied to other populations or age groups because it is based on Iraqi women aged 66 and older. Furthermore, because such data were unavailable, unobserved factors including personal medication habits and unreported health conditions, were not taken into account in our investigation. It was impossible to collect information on the drug usage of elderly breast cancer patients with metastatic disease. Future studies might be planned to get first-hand information that can address these concerns. The study did not include information on over-the-counter medications or pharmaceuticals covered by any other health insurance because it used data from Medicare drug data.

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