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Research Article

Incidence, patient characteristics and treatment patterns of early-stage triple-negative breast cancer (TNBC) in Bulgaria: A retrospective analysis based on real-world data

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Abstract

Breast cancer (BC) is the third most common cancer, making up 10.8% of cases in both men and women. In Bulgaria, it has the highest rates of diagnosis (23.3%) and death among women, with around 3558 new cases each year, 5–7% of which are attributed to triple-negative breast cancer (TNBC). This is lower than the global rate of 12–15%. The current 3-year non-interventional study aims to analyse newly diagnosed patients with a focus on the treatment patterns in both neo-adjuvant and adjuvant settings and to measure the time patients spent on treatment (real-world time of treatment, rwTOT) using secondary real-world data collected for other purposes. For the observed period, TNBC accounted for 5.2% of all breast cancer diagnoses, with peak ages of diagnosis ranging from 45 to 65 and 60 to 70, suggesting later-age diagnosis. Real-world data show a tendency for endocrine (letrozole, goserelin and tamoxifen) and targeted therapy (trastuzumab, pertuzumab/trastuzumab and bevacizumab) in eTNBC (early stage TNBC) patients, which is not fully compliant with the guidelines but suggests the possible presence of the so-called immunophenotypic triple-negative BC with very low expression levels of ER/PR (< 10–20%). The average rWToT for each of the years is approximately 3.60 months for adjuvant therapy and 3.6 for neoadjuvant therapy.

Keywords

early-stage triple-negative breast cancer, real-world data, treatment

Introduction

TAccording to GLOBOCAN data, breast cancer (BC) is the 3rd most common malignancy (10.8%) among both sexes and the type of cancer with the highest incidence (23.3%) and mortality rates among females in Bulgaria, with approximately 3558 newly diagnosed patients every year. (Globocan 2022) The percentage of triple-negative breast cancer (TNBC) patients in Bulgaria may vary significantly from the global incidence rate for this subtype

of BC (12–15%) and may account for not more than 5–7% of the total breast cancer patients (Dimitrova et al. 2021).

Generating real-world data and its practical value is crucial for clinical decision-making and healthcare and financial resource allocation.

TNBC is associated with poor outcomes in long-term situations. In this regard, providing appropriate time for therapy, especially in the early stages of the disease, is very important. As treatment patterns of TNBC are expected to change in the coming years, data from real-world therapeutic practice are valuable for achieving an individualised treatment approach. (Haiderali et al. 2021)

In recent years, in the publicly accessible and regularly updated national oncology registry in Bulgaria, a significant gap has emerged. This gap has impeded access to current and comprehensive data on cancer cases, treatment outcomes, and epidemiological trends, hindering the ability of healthcare professionals and policymakers to make informed decisions and implement targeted interventions. The lack of timely and reliable information in the oncology registry presents a concerning challenge in the effective management and surveillance of cancer across the country. This determined the need for the implementation of alternative sources of data collection. Real-world data and analyses included in the present study are expected to close some of the knowledge gaps in the epidemiology of TNBC in Bulgaria and thus contribute to a better understanding of the disease and its treatment patterns.

Methods and materials

Study design

This is a 3-year non-interventional retrospective database study on early-stage triple-negative breast cancer using secondary real-world data, collected for other purposes between 2019 and 2021.

Data collection and analysis were carried out using the Sqilline electronic artificial intelligence platform, Danny Platform (www.sqilline.com), which collects and aggregates anonymous data from more than 90% of the oncology practices on a national level. The platform is developed based on deep-learning natural language processing (DL-NLP) and provides information for disease staging and treatment ready for analysis. The scope of the data collection and analysis did not include any safety reconciliation, and informed permission was not necessary for the study.

Study population

The study population, included in the present study, consists of patients with triple-negative breast cancer (TNM Stages I, II, and III), diagnosed during the period of data collection (2019–2021).

Outcomes of interest

The primary objectives of the study are:

- To evaluate the number of newly diagnosed early-stage TNBC patients as a proportion of all newly diagnosed TNBC and all newly diagnosed BC patients for each of the years in the period 2019–2021;
- To analyse baseline demographic patient (age) and clinical (stage of diagnosis) characteristics among the selected cohort of patients.

Secondary objectives include:

- Analysis of the number of patients on neo-adjuvant and adjuvant therapy.
- Analysis of the preference for prescribed chemotherapy regimens in the neo-adjuvant and adjuvant settings.
- To calculate real-world time on treatment (rwTOT), measured as the length of time observed in real-world data (as distinct from controlled clinical trials) from initiation of systemic therapy to discontinuation of the treatment.

Statistical analysis

Results were evaluated through descriptive statistics on Excel v.2016 (average, SD and percentage data) and regression analysis on MedCalc to assess the link between TNM stage and rWToT and therapy line and rWToT.

Bias

Data from the Sqilline database reports represent more than 90% of all TNBC cases occurring in the healthcare system. Selection bias may be present to include patients who have ER, PR, and HER2 in case of false histology code or missing histology data. No histological or immunohistochemical revision was performed.

Misclassification and missing information are possible sources of bias. The results of the study must be interpreted in consideration of the known limitations of databases. The use of extracted data carries a possibility of information bias related to the validity of the data reported by the service providers, including missing, inconsistent or erroneous information.

Results

Primary outcomes

For the study period (January 2019–December 2021), the number of newly diagnosed breast cancer patients in Bulgaria is 11820. Out of them, 613 (5.2%) were newly diagnosed with TNBC, and 521 were in early-stage disease (Stage I, II, and III, eTNBC). The average age of eTNBC patients at the time of diagnosis is 57 (SD 14.67), varying from 55 in 2019 to 58 in 2021 (Table 1).

The results also show that the age at the time of diagnosis for the observed cohort of patients is mostly between 45 and 65, with a peak between 60 and 70 years of age, which shows a trend for a relatively late age at the time of diagnosis (Fig. 1).

Table 1. Patients' characteristics.

Newly diagnosed	2019	2020	2021	Total number
Total number of BC	4143	3832	3845	11820
Total number of TNBC (% of BC)	212 (5.12%)	196 (5.11%)	205 (5.33%)	613
Total number of eTNBC	160	175	186	521
The average age of eTNBC patients at the time of diagnosis	55 (SD 14.28)	57 (SD 15.75)	58 (14.60)	57 (SD 14.67)
Proportion of eTNBC out of TNBC	75.47%	89.29%	90.73%	84.99%
Proportion of eTNBC out of BC	3.86%	4.57%	4.84%	4.41%
TNM stage of eTNBC with prescribed therapy				
I	32	49	49	
II	57	79	75	
III	27	35	43	
Total	116	163	167	
TNM stage of eTNBC with initiated therapy	115	136	147	

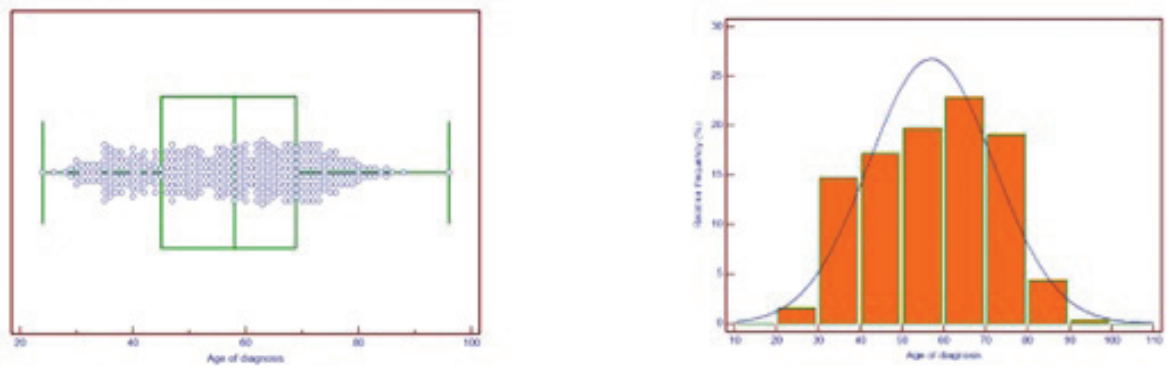

Figure 1. Box-and-whisker diagram and frequency distribution plot diagram of age at the time of diagnosis.

Secondary outcomes – treatment patterns

Treatment results are presented as:

– **Treatment preference** (based on oncology protocols, issued by the respective oncology commission) described as treatment setting and treatment type (Table 2).

The frequency analysis shows that adjuvant therapy is more frequently prescribed in TNM stage I and II, while neo-adjuvant therapy showed more frequent utilisation in TNM stage III (Fig. 2). It is worth noting that neoadjuvant therapy is prescribed at any stage of the disease, including stage I.

The preferred chemotherapy regime consists of anthracycline- and taxane-based treatments, used sequentially, which is the most often prescribed (neo)adjuvant therapy in most of the cases (Table 3).

Despite therapeutic guidelines being targeted, endocrine therapy was prescribed in 14 patients (eight with targeted and six with endocrine).

– **Real-world time on treatment (rWToT)** – presented rWToT as the length of time (in months) observed in real-world data (as distinct from controlled clinical trials) from initiation of systemic therapy to discontinuation of the treatment. The results from the average rWToT for each of the years from the observed period are based on hospital pharmacy records.

Table 2. Treatment preference in the selected cohort of eTNBC patients.

	2019	2020	2021
TNM stage I (NeoAdjuvant+Adjuvant)			
Therapy type			
Chemotherapy	27	46	45
Chemo + endocrine	0	0	0
Chemo+Targeted	0	1	1
Hormonal	2	1	0
Targeted	0	0	0
Therapy line			
Neoadjuvant	2	12	10
Adjuvant	27	34	35
TNM stage II (NeoAdjuvant+Adjuvant)			
Therapy type			
Chemotherapy	49	72	63
Chemo + Hormonal	0	0	0
Chemo+Targeted	3	0	3
endocrine	2	1	0
Targeted	1	0	0
Therapy line			
Neoadjuvant	6	22	30
Adjuvant	49	51	36
TNM stage III (NeoAdjuvant+Adjuvant)			
Therapy type			
Chemotherapy	19	27	35
Chemo + endocrine	1	0	0
Chemo+Targeted	1	0	0
Hormonal	0	0	0
Therapy line			
Neoadjuvant	10	19	26
Adjuvant	11	8	9

Table 3. Preferred therapeutic regimes as per hospital pharmacy records.

	TNM I	TNM II	TNM III	TNM I	TNM II	TNM III
	Adjuvant setting			Neo-Adjuvant setting		
Preferred chemotherapy regime						
Cyclophosphamide+Epirubicin+Fluorouracil	27	22		13	21	19
Cyclophosphamide + Docetaxel + Epirubicin	31	33	5		2	7
Cyclophosphamide + Docetaxel + Epirubicin+Fluorouracil	9					
Cyclophosphamide+Epirubicin		28	8		20	7
Carboplatin+Paclitaxel			6	5		19
Cyclophosphamide + Epirubicin (pharmorubicin) + Paclitaxel		10			4	
Targeted therapy						
Cyclophosphamide + Docetaxel + Epirubicin (Pharmorubicin) + Trastuzumab				1		
Docetaxel + Trastuzumab		1				
Cyclophosphamide + Docetaxel + Trastuzumab		1				
Cyclophosphamide + Docetaxel + Epirubicin (pharmorubicin) + Fluorouracil + Pertuzumab + Trastuzumab		1				
Bevacizumab + Paclitaxel		1				
Docetaxel + Pertuzumab + Trastuzumab			1		2	
Endocrine						
Tamoxifen	2					
goserelin+tamoxifen	1					
Anastrozole + Goserelin		1				
goserelin		1				
letrozole		1				

Table 4. Average rWToT for each of the years, depending on TNM stage and therapy type.

	TNM I (avg rWToT, months)		TNM II (avg rWToT, months)		TNM III (avg rWToT, months)	
	neoadjuvant	adjuvant	neoadjuvant	adjuvant	neoadjuvant	adjuvant
2019	5.00 (SD 1.84)	3.50 (SD 2.54)	3.74 (SD 2.98)	3.64 (SD 2.54)	3.68 (SD 2.65)	3.66 (SD 2.63)
2020	3.67 (SD 2.63)	3.64 (SD 2.54)	3.66 (SD 2.61)	3.64 (SD 2.53)	3.65 (SD 2.61)	3.76 (SD 2.81)
2021	3.63 (SD 2.62)	3.65 (SD 2.54)	3.66 (SD 5.29)	3.66 (SD 3.66)	3.65 (SD 2.55)	3.66 (SD 2.62)

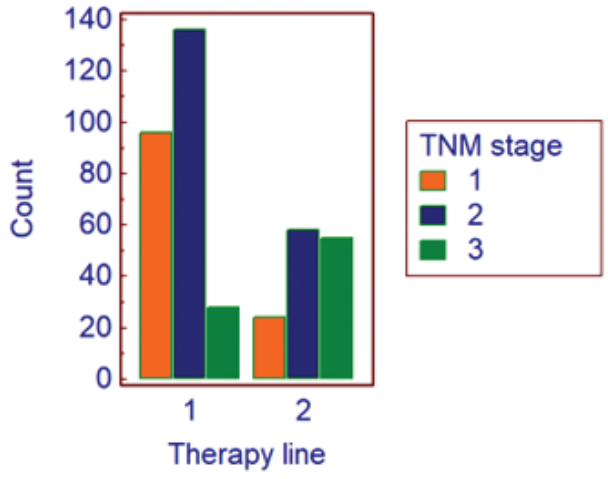

Figure 2. Frequency analysis of therapy line and TNM stage (1-adjuvant, 2-neo-adjuvant therapy).

The results are summarised in Table 4 for both types of therapy and TNM stage.

The average rWToT for each of the years is approximately 3.6 months for adjuvant therapy and 3.6 for neo-adjuvant therapy.

The results from the regression analysis show a correlation between the therapy line and rWTOT ($p = 0.015$), but such a correlation is not found for the TNM stage and rWTOT ($p = 0.338$) – Figs 3, 4.

Discussion

The incidence rate of TNBC among newly diagnosed breast cancer patients in Bulgaria, based on real-world data, is around 5%. Most of the patients (85%) are diagnosed in the early stages – Stage I, II and III. The average age of eTNBC patients at the time of diagnosis is 57 (SD 14.67), varying from 55 in 2019 to 58 in 2021. This increasing trend might be attributed to the restrictive measures during the COVID-19 pandemic. The latter also showed an impact on therapy initiation, especially in 2020 and 2021, in which 17% and 12% of the diagnosed patients, respectively, experienced a delay in the therapy onset. According to a study conducted by Poggio et al., patients diagnosed with triple-negative breast cancer (TNBC) faced delays of at least 4 months in receiving imaging tests and treatment delays of over 6 months. (Poggio et al. 2020) Brown and colleagues analysed how the

Dependent Y	Time_on_treatment__months_ Time on treatment (months)
Independent X	Therapy_line Therapy line

Sample size	397
Coefficient of determination R^2	0,01497
Residual standard deviation	2,1600

Regression Equation

$y = 4{,}2779 + -0{,}5586\ x$

Parameter	Coefficient	Std.Error	T-value	P
Intercept	4,2779	0,3253	13,1495	<0,0001
Slope	-0,5586	0,2280	-2,4498	0,0147

Analysis of Variance

Source	DF	Sum of Squares	Mean Square
Regression	1	28,0013	28,0013
Residual	395	1842,9710	4,6657

F-Ratio	6,0015
Significance level	P=0,015

Figure 3. Correlation between rWToT and therapy line (adjuvant/neo-adjuvant).

Dependent Y	TNM_stage TNM stage
Independent X	Time_on_treatment__months_ Time on treatment (months)

Sample size	397
Coefficient of determination R^2	0,002328
Residual standard deviation	0,7099

Regression Equation

$y = 1{,}8512 + 0{,}01576\ x$

Parameter	Coefficient	Std.Error	T-value	P
Intercept	1,8512	0,06797	27,2370	<0,0001
Slope	0,01576	0,01641	0,9600	0,3377

Analysis of Variance

Source	DF	Sum of Squares	Mean Square
Regression	1	0,4645	0,4645
Residual	395	199,0872	0,5040

F-Ratio	0,9215
Significance level	P=0,338

Figure 4. Correlation between rWToT and TNM stage.

COVID-19 pandemic has affected the timely diagnosis and treatment initiation in patients with triple-negative breast cancer (TNBC), which has been noted in our study population as well. They also emphasised the need for the development of specific guidelines to manage TNBC patients during COVID-19 outbreaks (Brown et al. 2021).

In recent years, research also analysed the possible role of AI-based tools in assisting molecular sub-typing, diagnosis and treatment, especially in aggressive tumours like TNBC, which treatment needs a more individualised approach (Batool et al. 2024).

We also believe that this is the first study in Bulgaria to specifically examine the real-world time it takes to treat triple-negative breast cancer. The findings indicate that the time required for treatment largely depends on the type of therapy and, for the period under observation, averages 3.65 months for both neo-adjuvant and adjuvant treatments for stages TNM I, II, and III. The analysis based on oncology protocols issued by the respective oncology commission showed that adjuvant therapy was the most frequently prescribed line of therapy in TNM Stage I and Stage II, while neoadjuvant therapy was predominant in TNM Stage III diagnosed patients. This trend is largely discussed in Bulgaria, but it is still lacking wider acceptance among medical oncologists. To our knowledge, only a few published studies are focusing on real-world time on treatment but in other localisations such as non-small cell lung cancer (Velcheti et al. 2022).

Treatment patterns follow the pharmacotherapeutic guidelines recommendations, as the most frequently prescribed regime was the sequential use of anthracycline followed by taxane or vice versa. Of note is the significant overuse of the regimen FEC despite the known recommendations to discourage this type of systemic therapy (reference NCCN, ESMO). These findings are in line with other published studies, according to which chemotherapy is the dominant treatment in the neoadjuvant and adjuvant settings (Giordano et al. 2013; Haiderali et al. 2021).

Real-world data, however, show a tendency for endocrine (letrozole, goserelin and tamoxifen) and targeted therapy (trastuzumab, pertuzumab/trastuzumab and bevacizumab) in eTNBC patients, which is not fully compliant with the pharmacotherapeutic guidelines. This may be due to the presence of the so-called immunophenotypic triple-negative BC with very low expression levels of ER/PR (< 10–20%) that sometimes may lead to the prescription of endocrine therapy in the adjuvant setting. Some studies, however, analyse possible pharmacological and molecular pathways which may affect TNBC. (van Barele et al. 2021; Kirkby et al. 2023) Such findings suggest that real-world data would foster a more individualised treatment approach based more on molecular mechanisms and specificities on an individual level, demanding the need for more studies with a focus on pharmacological and molecular profiling on oncology medicines (Malone et al. 2020).

The results of the study also show some important gaps that still need to be covered. The information in the database does not show the reasons for endocrine and targeted therapy choices. As the analytic database platform of Sqilline extracts the information directly from the patient's records, some data may be either missing from the records or not correctly stated. There are a lot of challenges related to processing data with missing parameters. Therefore, physicians need to enter the patient data correctly and fully and to be trained to work with digital health records (Kechagioglou 2023).

The study is conducted using data from the Sqilline database (structured data); therefore, the main limitation is the robustness of data recorded in the databases. Data from the Sqilline database reports represent more than

90% of all TNBC cases occurring in the healthcare system. Selection bias can occur to include patients who have ER, PR, and HER2. It is possible in the case of a false histology code or missing histology data. Misclassification and missing information are also possible sources of bias. The results of the study must be interpreted in consideration of the known limitations of databases.

Conclusion

The findings of this analysis demonstrated that TNBC treatment patterns are mainly consistent with worldwide standards and prior national studies. The study validated the importance of dynamic patient registers in conducting real-world studies of treatment trends. To better characterise and evaluate cancer, there is a need for a better registration system, on a national level, such as a National Cancer Registry.

Additional information

Conflict of interest

MSD Bulgaria compensated MJD for the conduction of the study, research and development of the manuscript. MVD is an employee of an MSD subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

All authors participate and contribute equally to this publication. The funding sponsor approved the study's design and the manuscript's final version. The sponsor had no role in the collection, analysis, or interpretation of data.

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Data availability

Data available on request from the authors.

References

Batool Z, Kamal MA, Shen B (2024) Advancements in triple-negative breast cancer sub-typing, diagnosis and treatment with the assistance of artificial intelligence a focused review. Journal of Cancer Research and Clinical Oncology150: 383. https://doi.org/10.1007/s00432-024-05903-2

Brown JM, Wasson MD, Marcato P (2021) Triple-negative breast cancer and the COVID-19 pandemic: Clinical management perspectives and potential consequences of infection. Cancers (Basel) 13(2): 296. https://doi.org/10.3390/cancers13020296

Dimitrova M, Milushewa P, Petrova E, Mihaylova M, Tzvetanova N, Petrova G (2021) Triple-negative breast cancer in Bulgaria: epidemiological data and treatment patterns based on real-world evidence and patient registries, Biotechnology & Biotechnological Equipment 35(1): 551–559. https://doi.org/10.1080/13102818.2021.1903338

Global cancer observatory (2024) Cancer today. Globocan: 2022: Bulgaria. https://gco.iarc.who.int/media/globocan/factsheets/populations/100-bulgaria-fact-sheet.pdf [Accessed on: March 2024]

Giordano SB, Jeruss JS, Bethke KP, Hansen NM, Khan S, Von Roenn J, Rosen S, Gradishar WL, Siziopikou KP, Meservey C, Kaklamani V (2013) Neoadjuvant Phase II trial with carboplatin and eribulin in triple negative breast cancer patients. Cancer Research 73(Suppl. 24). [Abstract P3-14-14] https://doi.org/10.1158/0008-5472.SABCS13-P3-14-14

Haiderali A, Rhodes WC, Gautam S, Huang M, Sieluk J, Skinner KE, Schwartzberg LS (2021) Real-world treatment patterns and effectiveness outcomes in patients with early-stage triple-negative breast cancer. Future Oncology 17(29): 3819–3831. https://doi.org/10.2217/fon-2021-0530

Kechagioglou P (2023) Big data in oncology: The electronic patient record transformation program. Seminars in Oncology Nursing 39(3): 151430. https://doi.org/10.1016/j.soncn.2023.151430

Kirkby M, Popatia AM, Lavoie JR, Wang L (2023) The Potential of hormonal therapies for treatment of triple-negative breast cancer. Cancers (Basel) 15(19): 4702. https://doi.org/10.3390/cancers15194702

Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL (2020) Molecular profiling for precision cancer therapies. Genome Medicine 12: 8. https://doi.org/10.1186/s13073-019-0703-1

Poggio F, Tagliamento M, Di Maio M, Martelli V, De Maria A, Barisione E, Grosso M, Boccardo F, Pronzato P, Del Mastro L, Lambertini M (2020) Assessing the impact of the COVID-19 outbreak on the attitudes and practice of italian oncologists toward breast. Annals of Oncology 31: S1017. https://doi.org/10.1016/j.annonc.2020.08.1804

van Barele M, Heemskerk-Gerritsen BAM, Louwers YV, Vastbinder MB, Martens JWM, Hooning MJ, Jager A (2021) Estrogens and progestogens in triple negative breast cancer: Do they harm? Cancers (Basel) 13(11): 2506. https://doi.org/10.3390/cancers13112506

Velcheti V, Hu X, Li Y, El-Osta H, Pietanza MC, Burke T (2022) Real-world time on treatment with first-line pembrolizumab monotherapy for advanced NSCLC with PD-L1 expression ≥ 50%: 3-year follow-up data. Cancers (Basel) 14(4): 1041. https://doi.org/10.3390/cancers14041041