

Table 2: EORTC QLQ-C30 and QLQ-BR23 scores by age.

	<60 years		≥60 years		p-value
	Mean	SD	Mean	SD	
QLQ-C30					
Global health status	65.2	24.1	66.3	22.7	0.83
Functional scales					
Physical functioning	74.7	19.2	73.3	20.8	0.732
Role functioning	74.6	26.2	77.1	24.9	0.635
Emotional functioning	73.5	20.5	75.4	18.4	0.644
Cognitive functioning	74	27.3	81.3	18.9	0.125
Social functioning	82.2	26.5	96.3	11	0.001
Symptom scales					
Fatigue	27.5	25.7	21.4	20.8	0.201
Nausea and vomiting	4.1	11.5	2.5	11.7	0.505
Pain	24.9	24.8	26.7	32.4	0.767
Dyspnea	6.4	16	9.2	21.3	0.472
Insomnia	40.9	32.7	33.3	35.4	0.279
Appetite loss	9.4	20.7	10.8	26.6	0.759
Constipation	11.1	19.2	5.8	12.8	0.109
Diarrhea	2.9	11.4	5.8	18.3	0.338
Financial difficulties	18.1	26	16.7	32.9	0.808
QLQ-BR23					
Functional scales					
Body image	79.2	23.5	89.6	19.9	0.026
Sexual functioning	15.2	19.2	4.6	13.1	0.002
Sexual enjoyment	39.1	19.2	33.3	23.6	0.561
Future perspective	50.9	30.9	62.5	30.4	0.07
Symptom scales					
Systemic therapy side effects	17	16.3	12.6	14.8	0.176
Breast symptoms	14.6	17.1	8.5	14.1	0.068
Arm symptoms	23	21.8	25.8	27.7	0.575
Upset by hair loss	11.1	16.7	44.4	34.4	0.025

SD, standard deviation

Around one-third of patients (34%) acknowledged financial difficulties associated with their physical condition or treatment. The global health status of patients was generally good, with a mean overall health rate of 4.9 and a mean QoL rate of 5 on a 7-point Likert-type scale.

EORTC QLQ-BR23

The application of the EORTC QLQ-BR23 questionnaire, concerning patients' self-assessment of their body image, showed that most women did not feel physically less attractive (68%), had no difficulty looking at their naked body (69%), and did not feel less feminine (70%) as a result of the disease or its treatments (Supplementary Tables 3 and 4). Concern about the future was the main worry for these patients (80%),

with 12% reporting great concern. Regarding sexuality, most women had not been sexually active (71%) or felt sexual desire (72%) in the previous four weeks. Among those who were sexually active, 3 out of 4 had no enjoyment in sexual intercourse. A relevant proportion of patients experienced local symptoms related to BC or its treatments. More than half (58%) experienced pain in the arm or shoulder, 32% hand or arm edema, 48% difficulty raising the arm, 42% pain in the affected breast area, and 11% edema in the affected breast area.

Quality of life by patient subgroup

Age

QoL according to age (<60 vs. ≥60 years old) is depicted

in **Table 2**. Younger BC patients (<60 years old) reported significantly worse social functioning ($p=0.001$) and were less happy with body image ($p=0.026$) and more upset by hair loss ($p=0.025$). On the other hand, they reported better sexual functioning ($p=0.002$).

Supplementary Table 5 depicts QoL scores according to monthly household income ($\leq 1200\text{€}$, $1201\text{-}2000\text{€}$ and $>2000\text{€}$). Low income ($\leq 1200\text{€}$) was associated with worse physical functioning ($p=0.002$) and greater financial difficulties ($p=0.029$) compared to higher monthly income ($>2000\text{€}$). However, only the differences between a monthly household income $\leq 1200\text{€}$ and $>2000\text{€}$ were significant.

Disease stage

The stage of BC affected women's QoL, with women with advanced disease experiencing poorer global health status ($p=0.008$), physical functioning ($p=0.003$), role functioning ($p=0.013$), and cognitive functioning ($p=0.0012$), and higher levels of pain ($p=0.006$) and systemic therapy side effects ($p=0.023$) compared to women in earlier stages of disease (**Table 3**). On the other hand, advanced disease stage was not significantly associated with worse symptoms (other than pain) or worse sexual functioning/enjoyment, and also did not influence patients' future perspective.

Table 3: EORTC QLQ-C30 and QLQ-BR23 scores by disease stage.

	Localized and locally advanced BC		Metastatic BC		p-value
	Mean	SD	Mean	SD	
QLQ-C30					
Global health status	70	19.4	50	30.2	0.008
Functional scales					
Physical functioning	76.9	17.7	62.9	22.5	0.003
Role functioning	78.5	23	62.7	31.1	0.013
Emotional functioning	75.3	19.8	65.9	22	0.063
Cognitive functioning	80.1	21.4	65.1	29.8	0.012
Social functioning	90.3	20.9	81	25.4	0.09
Symptom scales					
Fatigue	23.1	21.6	35.4	29.5	0.087
Nausea and vomiting	1.9	6.6	9.5	20.8	0.11
Pain	22.2	26.7	41.3	30.1	0.006
Dyspnea	6	18	12.7	19.7	0.146
Insomnia	36.1	33.5	47.6	34.3	0.171
Appetite loss	8.8	21.7	12.7	26.8	0.494
Constipation	9.3	18.7	11.1	16.1	0.682
Diarrhea	2.8	9.3	9.5	26.1	0.258
Financial difficulties	16.2	29.1	23.8	30.1	0.298
QLQ-BR23					
Functional scales					
Body image	83.8	23.1	82.5	21.7	0.825
Sexual functioning	8.8	17.2	15.1	14.8	0.134
Sexual enjoyment	41.2	18.7	29.6	20	0.157
Future perspective	56	30.6	52.4	34.3	0.642
Symptom scales					
Systemic therapy side effects	13.4	13.9	22.4	20.9	0.023
Breast symptoms	11.1	16.3	15.5	16.7	0.285
Arm symptoms	22.2	24.2	30.7	25.8	0.169
Upset by hair loss	23.1	28.5	22.2	38.5	0.965

BC, breast cancer; SD, standard deviation

Treatment modality

Regarding the type of breast surgery, women who underwent mastectomy had better QoL in terms of symptoms as dyspnea ($p=0.017$) and loss of appetite ($p=0.033$), financial difficulties ($p=0.048$), and sexual enjoyment ($p=0.035$; **Table 4**). On the other hand, they were more upset about hair loss ($p=0.035$). Patients not submitted to radiotherapy had better global health status than those who did ($p=0.046$). On the other

hand, no differences were found in breast or arm symptoms (**Supplementary Table 6**). Considering women submitted to chemotherapy, and regardless of the setting (neoadjuvant/ adjuvant), these experienced significantly more nausea and vomiting ($p=0.006$), with no significant differences in the remaining aspects assessed (**Table 5**). Women treated with endocrine therapy were less upset by hair loss ($p=0.016$) and suffered less from constipation than those not receiving endocrine therapy ($p=0.031$; **Table 6**).

Table 4: EORTC QLQ-C30 and QLQ-BR23 scores by type of breast surgery.

	Type of breast surgery				p-value
	Mastectomy		Conservative surgery		
	Mean	SD	Mean	SD	
QLQ-C30					
Global health status	67.9	21.8	62.3	25.8	0.271
Functional scales					
Physical functioning	74.8	18.4	74.4	21.9	0.943
Role functioning	80.9	23.8	71.8	26.9	0.097
Emotional functioning	76.8	20.5	70.4	18.2	0.129
Cognitive functioning	78.7	22.7	75	27.1	0.483
Social functioning	86.9	23.6	87.7	23.3	0.87
Symptom scales					
Fatigue	19.9	21.5	29.4	26.1	0.063
Nausea and vomiting	3.5	12	4	12.1	0.869
Pain	23	24.2	28.6	31.5	0.354
Dyspnea	2.1	8.2	10.3	20.1	0.017
Insomnia	36.2	30.2	39.7	36.2	0.623
Appetite loss	4.3	13.2	15.1	29.6	0.033
Constipation	6.4	16.5	10.3	17.2	0.275
Diarrhea	5.7	17.5	3.2	12.3	0.443
Financial difficulties	12.8	25.6	25.4	32.8	0.048
QLQ-BR23					
Functional scales					
Body image	78.9	24	87.9	20.3	0.061
Sexual functioning	14.2	20.6	7.1	13.3	0.056
Sexual enjoyment	43.1	19.6	29.6	11.1	0.035
Future perspective	60.3	30	47.6	31.4	0.055
Symptom scales					
Systematic therapy side effects	13.7	12.8	16.1	18.6	0.482
Breast symptoms	10.3	12.6	14.7	20.2	0.228
Arm symptoms	22.2	21.9	25.4	25.4	0.528
Upset by hair loss	44.4	34.4	9.5	16.3	0.035
SD, standard deviation					

Table 5: EORTC QLQ-C30 and QLQ-BR23 scores by chemotherapy as treatment modality.

	Chemotherapy				p-value
	No		Yes		
	Mean	SD	Mean	SD	
QLQ-C30					
Global health status	73.7	18.7	63.7	24.4	0.099
Functional scales					
Physical functioning	79.3	19.7	73.3	19.7	0.242
Role functioning	82.5	23.2	74.6	26	0.231
Emotional functioning	72.4	23.4	74.1	19.7	0.739
Cognitive functioning	84.2	18.8	75.2	25	0.147
Social functioning	89.5	25.6	87.5	22.1	0.737
Symptom scales					
Fatigue	21.1	21.6	25	23.9	0.514
Nausea and vomiting	0	0	4.2	12.8	0.006
Pain	24.6	29.6	25.7	27.1	0.877
Dyspnea	7	14	6.1	16.1	0.828
Insomnia	35.1	34.2	38.2	33.4	0.722
Appetite loss	12.3	27.7	8.3	21.2	0.497
Constipation	8.8	18.7	9.2	17.7	0.924
Diarrhea	1.8	7.6	4.8	16.1	0.421
Financial difficulties	15.8	32.1	19.7	29.9	0.613
QLQ-BR23					
Functional scales					
Body image	85.1	23.2	82.7	22.7	0.681
Sexual functioning	8.8	16.1	11.2	18.1	0.598
Sexual enjoyment	33.3	23.6	39.4	19.6	0.552
Future perspective	52.6	30.1	55.7	31.5	0.702
Symptom scales					
Systematic therapy side effects	13.5	14	15.5	16.2	0.633
Breast symptoms	11.8	16.7	11.8	16.3	1
Arm symptoms	20.5	27.8	23.8	22.3	0.578
Upset by hair loss	11.1	19.2	27.3	32.7	0.437
SD, standard deviation					

Table 6: EORTC QLQ-C30 and QLQ-BR23 scores by endocrine therapy as treatment modality.

	Endocrine therapy				p-value
	No		Yes		
	Mean	SD	Mean	SD	
QLQ-C30					
Global Health Status	65.9	21.6	65.3	28.5	0.913
Functional scales					
Physical functioning	74.9	18.3	72.5	23.9	0.612
Role functioning	76.6	24.7	73.6	28.6	0.624
Emotional functioning	74.1	21.2	72.6	17.6	0.75
Cognitive functioning	76.8	24.5	77.1	24	0.961
Social functioning	90.1	20.4	81.9	27.3	0.123
Symptom scales					
Fatigue	24.5	23.3	26.9	25.6	0.673
Nausea and vomiting	1.8	8.1	8.3	17.7	0.092
Pain	27.3	30.2	22.2	21.2	0.371
Dyspnea	7.2	18.5	8.3	17.7	0.794
Insomnia	37.8	33.3	37.5	35.9	0.966
Appetite loss	8.1	21.2	15.3	27.8	0.255
Constipation	11.3	19.3	4.2	11.3	0.031
Diarrhea	3.2	11.3	6.9	21.9	0.423
Financial difficulties	20.3	30.6	12.5	27.5	0.271
QLQ-BR23					
Functional scales					
Body image	85.7	20.9	77.4	85.7	0.119
Sexual functioning	9.7	17	13.9	9.7	0.312
Sexual enjoyment	35.1	20.7	44.4	35.1	0.248
Future perspective	56.3	32.6	51.4	56.3	0.508
Symptom scales					
Systemic therapy side effects	13.9	14.8	20.4	13.9	0.081
Breast symptoms	11.8	16.8	12.5	11.8	0.859
Arm symptoms	23.3	24.5	25.9	23.3	0.645
Upset by hair loss	10	16.1	44.4	10	0.016

SD, standard deviation

Discussion

With breast cancer becoming a largely curable disease and a substantial proportion of patients becoming long survivors, much due to early detection programs and increased treatment effectiveness, QoL after cancer has evolved to be one of the cornerstones of the patient journey. However, the current follow-up standards fall short of adequately addressing this crucial aspect of patients' management. According to a study presented at the ESMO Breast Cancer Virtual Congress 2021, BC survivors widely differ in the burden of symptoms they experience after the end of treatment, and therefore post-treatment care should be tailored to address each survivor's unique experiences and needs [33]. The evidence in the literature is scarce regarding the management

and quality of care of BC in Portugal [24]. Since real-world data is necessary to assess and improve the outcomes of these patients, H360 intended to address this unmet need by providing a comprehensive, overall picture of BC management in the country. One of its fundamental aspects is patients' QoL, which the present study sought to investigate. The authors applied two of the most widely used instruments for assessing health-related QoL in patients with cancer, EORTC QLQ-C30 and its specific BC module QLQ-BR23, as several studies have validated and employed these scales and they are also validated in Portugal [27, 34–38]. Women's global health status was good, with a mean overall health rate of 4.9 and a mean QoL rate of 5 on a 7-point Likert-type scale. However, similarly to previous studies, some level

of impairment was seen in strenuous activities (reported by 84% of women) or taking a long walk (reported by 64% of women) [37,39]. Psychosocial effects were among the most reported by BC patients, with 71% experiencing some degree of concern, 67% having difficulty remembering things, 57% feeling irritability, and 47% reporting feelings of depression. This percentage of psychosocial effects is higher than what had been described in French studies (around 30%) [11,19]. The difficulties reported in strenuous physical activities and long walks may be associated with symptoms like asthenia induced by chemotherapy or with psychological aspects, as difficulty sleeping (66%) and tiredness (57%), also common in these patients. Another study reported a prevalence of severe global fatigue after treatment of 35.6%, and that it endures for years [40]. This should be addressed in the follow-up of BC survivors, as it has a potentially significant detrimental impact on patients' QoL. Psychological monitoring, downgraded for far too long, may have a key role in this context [21,41].

Pain was the most frequent symptom reported by BC survivors (57%) and interfered with daily activities in 46%. This figure is similar to what had been reported in another study (51%) [11]. Several explanations can be put forward to justify such a high prevalence of this symptom: it may be undervalued by doctors; patients may fail to mention it in consultation due to the reduced time of medical appointments; patients may think that pain is a normal symptom given their clinic situation; and/or patients may focus their attention on disease prognosis and neglect QoL.

Approximately one-quarter of patients in this study considered that social and family activities were impaired due to the disease and its treatments (23% and 26%, respectively), which may be related to the high percentage (71%) that reported psychological effects, including increased levels of depression and irritability. More than half of patients (56%) referred that BC and its treatments had an impact on work and daily activities. This raises awareness of the need for developing and implementing alternative working options for BC survivors, such as part-time and/or remote working or adjusting schedules in a way that allows these patients to maintain their work activity while undergoing or recovering from the disease and its treatments. According to data in the literature, two years after BC diagnosis, 21% of patients had not returned to work yet [19]. This evidence reinforces the need for alternative working options or even changes in professional field that can accommodate the new limitations imposed by the disease. Although hospital care and anticancer oral medications are free of charge in the Portuguese public service, and the proportion of reimbursement due to medical leave is high, 34% of patients in this study reported financial difficulties. This percentage might be explained by the high proportion of people in temporary or precarious working situations in Portugal, with consequently low social security

protection. The precarious socioeconomic status of these patients is also suggested by the low monthly household income ($\leq 1200\text{€}$) reported by 34% of study participants. Most patients reported not feeling physically less attractive (68%), having no difficulties looking at their naked body (69%), and not feeling less feminine (70%) due to BC. This may in part be due to the comprehensive range of solutions that are currently available for BC survivors, such as wigs and scarves, and eventually also to the fact that BC surgery is increasingly moving from mutilating procedures to breast-conserving and reconstructive ones. Breast reconstruction is now a free option in public hospitals, although not always possible at the same time of mastectomy, as others have also reported [42]. Younger women (<60 years) in this study reported worse social functioning. Although speculative, this may be explained by their previously more active life compared to older women, making them notice a greater impact of the disease, or by having been submitted to more aggressive treatments. Concerns with body image and hair loss were also aggravated in younger women. A total of 71% were sexually inactive, which is a very high percentage compared to the 23.9% reported elsewhere [43]. However, when assessing sexual functioning according to age, it was better in the age group below 60 years, in agreement with another study [8]. It would have been interesting to compare the periods before and after treatment to draw further conclusions, as it is acknowledged that undergoing chemotherapy or endocrine therapy has a great impact in sexual functioning [11], and even potentially impact treatment adherence. As expected, low socioeconomic status was associated with aggravated financial difficulties, but a curious finding was that it also had worse score in the physical functioning scale. This study showed that the stage of BC affects patients' QoL, with women with advanced disease experiencing worse global health status, worse physical, role, and cognitive functioning, and more pain and side effects from systemic therapy than women with localized/locally advanced disease. Although the association of more advanced disease stages with poorer QoL was to be expected, others have reported that women with early BC attain higher levels of emotional distress, experiencing anxiety, depression, and irritability, with an impact on QoL compared to women with advanced BC [44–46]. This indicates that, regardless of the stage of disease, it always carries a non-negligible burden in patients' QoL. The body of evidence retrieved from this study and from previous ones suggests that the routine assessment of BC patients' QoL should be incorporated into the clinical practice through the application of Patient-Reported Outcome Measures (PROMs), ideally before, during and after BC treatment.

Study limitations

This study had some limitations that should be acknowledged. Participants' level of literacy may represent a

study limitation, as the questionnaires applied required some level of understanding and literacy from respondents, which was not ensured. On the other hand, due to its cross-sectional nature, the study did not take into account the fact that patients were in different stages of treatment, with some possibly even having finished treatment already. According to the literature, QoL in some patient clusters increases throughout treatment and follow-up, suggesting that patients adapt fairly well to the disease and its treatments [47, 48]. However, the cross-sectional design of this study did not allow to explore this issue. Finally, the limited number of patients included in the study due to initial bureaucratic issues and delays in the response of Ethic and Data Protection Commissions, which precluded the inclusion of more hospitals in the study, and to logistic difficulties in contacting patients by telephone or email, represents another study limitation that may weaken its external validity. Despite these limitations, this study provides novel and valuable insights into the QoL of BC patients and survivors in Portugal and should be used as a starting point for the development and implementation of measures accordingly.

Conclusion

The results of this study suggest that more attention should be paid to the unmet needs of BC survivors. The EORTC QLQ-C30 and QLQ-BR23 scales can be valuable instruments to adopt in the patient's journey to assess their QoL and thereby increase health professionals' awareness of the points to improve to optimize their long-term outcomes.

Hopefully, this study will be a starting point for improving the personalized survivorship care of BC patients in Portugal. This includes but is not limited to referring patients to appropriate follow-up interventions, including physical, psychosocial, and lifestyle support, in addition to purely clinical. Patients' referral to medical social workers and appropriate support services may also provide them with the necessary resources to reduce the financial burden of healthcare. The authors believe that this study makes a relevant contribution to improving BC care in Portugal and will substantiate and strengthen the application of preexisting specific guidelines that are still not routinely used in the clinical practice.

Declarations

Ethics Approval And Consent To Participate

This study was approved by the Administration Boards of participating hospitals, following approval by the respective Ethics Committees. It was also approved by the Portuguese National Data Protection Commission (CNPD).

Study design and conception were of the strict responsibility of study investigators.

All patients signed written informed consent prior to study enrolment.

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Statements and Declarations

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Patrícia Miguel Semedo, Sara Coelho, Inês Brandão Rêgo, Laetitia Teixeira, Susana Sousa, and Francisco Pavão. The first draft of the manuscript was written by Patrícia Miguel Semedo, Sara Coelho, and Inês Brandão Rêgo and all authors commented on previous versions of the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability

The dataset generated and analyzed in the current study is not publicly available due to European Union general data protection regulations. They can be provided by the corresponding author, upon reasonable request, after approval by the local Government responsible for assessing the impact on data protection and by the study's Institutional Ethics Committees.

Ethics Approval

This study was approved by the Administration Boards of participating hospitals following approval by the respective Ethics Committees. The study's design and conception were of the strict responsibility of study investigators. All methods were performed in accordance with the relevant guidelines and regulations in accordance with the Declaration of Helsinki.

Consent to Participate

All patients provided written informed consent prior to any study-specific procedure.

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