Journal Pre-proof

COVID-19 Incidence and Mortality in Patients Operated on for Breast Cancer. Comparison with the General Population.

Israel Barco , Carolina Chabrera , Antonio García-Fernández , Manel Fraile , Carmen Vidal , Claudia Beatriz Mitru , Oriol Porta , Marc García-Font

PII: S1526-8209(22)00247-6
DOI: https://doi.org/10.1016/j.clbc.2022.11.002
Reference: CLBC 1532

To appear in: *Clinical Breast Cancer*

Received date: Jun 28, 2022
Revised date: Nov 8, 2022
Accepted date: Nov 11, 2022

Please cite this article as: Israel Barco , Carolina Chabrera , Antonio García-Fernández , Manel Fraile , Carmen Vidal , Claudia Beatriz Mitru , Oriol Porta , Marc García-Font , COVID-19 Incidence and Mortality in Patients Operated on for Breast Cancer. Comparison with the General Population., *Clinical Breast Cancer* (2022), doi: https://doi.org/10.1016/j.clbc.2022.11.002

HIGHLIGHTS

- BC patients had higher incidence of COVID-19 infection and mortality compared to control group (13.1% vs 11.7% and 7.1% vs 4.7%)
- Mortality rates were higher in nursing home patients older than 70 years, and mainly happened during the first six months of the pandemic event.
- Distant metastases and living in a care home were the only independent predictive factors for COVID-19 mortality in BC patients.

COVID-19 Incidence and Mortality in Patients Operated for Breast Cancer. Comparison with the General Population

COVID-19 Incidence and Mortality in Patients Operated on for Breast Cancer. Comparison with the General Population.

Israel Barco[1], MD; Carolina Chabrera[2], PhD, MSN, RN; Antonio García-Fernández[3], PhD, MD; Manel Fraile[4], PhD, MD; Carmen Vidal[5], CNM, RN; Claudia Beatriz Mitru[6], MD; Oriol Porta[7], MD, PhD; Marc García-Font[8], PhD.

Author Affiliations:

[1] Breast Unit, Departament of Gynecology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona.
ORCID: https://orcid.org/0000-0003-3520-8736

[2] Tecnocampus, Universitat Pompeu Fabra, Research Group in Attention to Chronicity and Innovation in Health (GRACIS), Mataró, Barcelona, Spain.
ORCID: http://orcid.org/0000-0002-1661-7916

[3] Head emeritus Breast Cancer Screening Vallés Occidental West. Barcelona. Breast Unit University Hospital Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona. Barcelona, Spain.
ORCID: https://orcid.org/0000-0002-8236-0952

[4] Head emeritus Nuclear Medicine Departament, University Hospital Mútua Terrassa and University Hospital German Trias i Pujol, Barcelona, Spain.

[5] Department of nursing, Breastfeeding Consultant, Institut Català de la salut, Barcelona Spain.

[6] Breast Unit, Departament of surgery University Hospital Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona. Barcelona, Spain.

[7] Departament of Gynecology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona.

[8] University International of Catalunya, Barcelona, Spain.
ORCID: https://orcid.org/0000-0002-1280-9611

Corresponding Author:

Carolina Chabrera PhD, MSN, RN
School of Health Sciences TecnoCampus, Pompeu Fabra University, Ernest Lluch 32, 08032 Mataró, Spain
Email: cchabrera@tecnocampus.cat

ABSTRACT

Background

Breast Cancer remains the most commonly diagnosed malignancy and the most common cause of cancer-related mortality in women worldwide. Covid-19 mortality in BC patients has been linked to comorbid conditions rather than to cancer treatment itself, although this was not confirmed by a meta-analysis. Also, during Covid-19 outbreaks, a great deal of health care resources are reassigned to critical Covid-19 patients.

Patients and methods

During five consecutive trimesters (from 1/12/2020 to 31/3/2021) 2,511 breast cancer (BC) patients older than 20 years from our institution were surveyed. 1,043 of them had received a Covid test and these made our study group, which was conveniently compared with the Covid-19 tested background feminine Catalan population.

Results

13.1% of our patients presented with a positive Covid-19 test, whereas confirmed COVID-19 infection amounted to 7.1% of the feminine Catalan tested population. The COVID-19-specific mortality rate was 11.7% (16/137) in the study group, which compares with a 4.7% rate for the overall population. Most deaths occurred in patients over 70.

Conclusions

Three clinical factors were significantly associated with Covid-19 mortality in BC, namely lack of hormone therapy, distant metastases, and BC dwelling in

nursing homes. BC patients are at a higher risk of Covid-19 infection and mortality in comparison with the reference group without BC.

MICRO ABSTRACT

1,043 breast cancer patients (BC) had a Covid test and made our study group, which was conveniently compared with the COVID-19 tested background feminine Catalan population.

Covid-19 incidence and mortality were indeed higher among BC patients, although BC per se without metastases was not linked to increased mortality.

Metastases and nurse home dwellings were significantly associated with mortality.

Keywords: Breast neoplasms, Covid-19, Survival, Nursing homes, comorbidity.

Background

Some reports in the literature initially suggested that, within the present Covid-19 pandemic crisis[1], patients with a history or with active malignant disease were at higher risk of getting infected, as well as of developing Covid-19-related complications[2-4] However, such reports were often limited by short sample size, or by being restricted to a specific geographical area, and therefore their findings could not be easily extrapolated to the general population of cancer patients[4]. The notion that cancer patients are at a higher risk for Covid-19 has been further supported by additional research[5-9]. On the other hand, it has been shown that cancer patients infected by the SARS-COV2 virus tend to develop an antibody response similar to that of previously healthy subjects[10].

Breast Cancer (BC) is indeed both the most commonly diagnosed malignancy and the most common cause of cancer-related mortality in women worldwide[11].

A fresh report suggested that Covid-19 mortality rates in BC patients were related to comorbid conditions, rather than to cancer treatment itself[12], although such results were not confirmed by a subsequent meta-analysis[13].

Also, it is acknowledged that, during Covid-19 outbreaks, a great deal of healthcare resources is reassigned to critical Covid-19 patients[14].

Singh MK et al.[15] were able to show that basal ACE2 receptor (angiotensin-converting enzyme type 2 receptor) cell expression was significantly increased in several conditions, including leukemia, lung, breast, or cervical cancer, as well as in non-alcoholic fatty liver, psoriasis, and hospital-acquired pneumonia. Increased cell ACE2 receptor expression may enhance viral cell invasion and thus, explain greater susceptibility for SARS-CoV-2 infection in patients with such conditions.

Furthermore, often patients with malignancies are older, mostly over 60, and sustain significant comorbidities, which in themselves lead to a greater risk of Covid-19-related morbidity and mortality[16]. Increased Covid-19 mortality rates seem associated with factors such as disease severity, lack of specific treatment, and, perhaps strained medical resources due to increased Covid-19 hospital admissions. Notwithstanding the importance of such factors, there is however some uncertainty regarding other factors that may lead to worsened clinical outcomes in cancer patients.

We aimed at tracing the characteristics and outcomes of both outpatient and hospital-admitted Covid-19 sufferers with a history or with actively treated BC at our Breast Unit.

PATIENTS AND METHODS

Study design. It was conceived as a unicentric cross-sectional, retrospective analysis.

As such, it was approved by the Hospital Universitari Mutua de Terrassa Review Board (Nº O/21-094) under the consideration that it was dealing with an active population challenge.

Patients. The study group included patients aged over 20 with previous or active BC who were tested for Covid-19. Patients with both invasive and in situ tumors were included. These were compared with women from the general population receiving a SARS-CoV-2 test by the Catalan Health Service. The study was meant to span the whole year 2020 and the first trimester of 2021. The actual data collecting time window was from December 1, 2020, to March 30, 2021. Individual subject data were derived from the clinical records of our center, as well as from the online shared clinical record service of the Catalan Health Service and the official population statistical source service. (https://www.idescat.cat/ [Last consulted 10th January 2022]).

The Breast Unit database was refurbished to include certain Covid-19-related variables, including the SARS-CoV-2 test (CoT), either polymerase chain reaction (PCR) or rapid antigen lateral flow test (RT), date of CoT, patient age at CoT, the reason to test, type of CoT, CoT result, covid signs/symptoms in positive CoT subjects, and mortality, stating if at home or nursing home.

Statistics

Qualitative variables were expressed as numbers and percentages, while quantitative variables were expressed as mean value and standard deviation. For comparison of qualitative variables, the Chi-square test or the Fisher's exact test was used, while for comparison of mean values the ANOVA test was used. Statistical significance was set at a $p<0.05$ value, with a two-tailed approach. Data were subjected to a univariate and multivariate logistic regression analysis using the SPSS statistical software v23.0 (SPSS Inc., Chicago, IL, USA). As the predictive criterion, we considered a dichotomy variable defining mortality after COVID-19. Adequacy of model fitting was measured using the Hosmer–Lemeshow test. The predictive variables eventually used in our logistic regression (LR) model were those variables shown to be statistically significant in the univariate analysis.

RESULTS

Of the total 2,511 BC patients older than 20 that were registered in our database, 1,043 (41.5%) received at least one CoT. The total number of CoT was 1,833, 1,180 of which were PCR tests and 653 RT. The reference group included 2,625,958 women with a CoT.

COVID-19 Incidence. Confirmed Covid-19 infection amounted to 137 subjects out of 1,043 BC cases (13.1%), whereas confirmed Covid-19 infection amounted to 7.1% of the feminine Catalan tested population, a statistically significant difference ($p < 0.001$). Table 1 shows the univariate analysis results of COVID-19 comorbidity factors in BC subjects.

COVID-19 Specific Mortality. The covid-19-specific mortality rate was 11.7% (16/137) in the study group, which compares with a 4.7% rate for the overall population, a statistically significant difference ($p < 0.001$).

Table 2 shows statistically significant factors for Covid-19 mortality according to the univariate analysis. These included age over 70, BMI, tumor phenotype, distant metastases, lack of hormone therapy, and being a resident in a nursing home. Of note, most deaths occurred in non-smokers and abstemious women, both probably related to patient age. Variables that turned out significant in the univariate analysis were used as the base for the multivariate analysis, after which only distant metastases, lack of hormone therapy, and living in a nursing home kept their independent significance (Table 6).

Age and COVID-19 Mortality. Most COVID-19 deaths occurred beyond 70 years of age, both in the study group and in the reference group, with no statistical difference (P=0.55). As for patients under 70, Covid-19 mortality was 0.8% in the reference group, and 6.3% in the study group, a statistically significant difference ($p < 0.001$), Table 3.

COVID-19 Mortality time-spread. Table 4 shows mortality rates at trimestral intervals. It can be seen that Covid-19 mortality occurred mostly during the first two trimesters of 2020 and was significantly higher for the study group ($p < 0.001$).

COVID-19 Home deaths vs Nursing Home deaths. The mortality rate for subjects in the study group living in nursing homes was 12.5% (8/64), which

was significantly higher than for patients living in their own homes, with a death rate of only 0.8% (8/978). This was a significant difference (p<0.001) both in the univariate and multivariate analyses (Tables 4 and 6).

Along the first five trimesters, the Covid-19 mortality rate in nursing home residents from the reference population was 26.7%, (5,568/20,818) whereas the corresponding mortality rate for patients with BC was 40% (8/20), a non-statistically significant difference (p =0.181).

COVID-19 Incidence and Mortality rates in Infiltrating vs In Situ Carcinoma patients. The rate of Covid-19 infections was 12.8% (121/948) in patients with infiltrating carcinoma (IC), whereas such incidence was 16.8% (16/95) in patients with DCIS; a nonsignificant difference (P=0.167). Covid-19 mortality rate was 1.6% (15/948) in IC patients and 1.1% (1/95) in CDIS patients, also a non-significant difference (p=0.564). On the other hand, both groups were homogeneous when age was considered: a mean of 56.2 ±12 years (range 22-91) for IC patients, and 56±9 years (range 30-86) for DCIS patients. Also, when nursing home dwelling was considered: 6.3% (60/948) for IC patients vs 4.2% (4/95) for DCIS patients (p=0.288).

COVID-19 Mortality and Adjuvant Hormone Therapy. Indication of hormone therapy in our patients relies on the individual molecular subtype and only applies to those with tumors expressing estrogen and progestin receptors. BC patients not receiving hormone therapy showed a significantly higher Covid-19 mortality rate than those receiving hormone therapy, both in the univariate and multivariate analysis (4.2% vs 1.1%) (p = 0.015). Tables 1 and 6. More broadly, patients with a positive hormone receptor (HR) status showed a 1% (9/808) mortality rate, while patients with a negative HR status (Pure Her2 and TN subtypes) showed a covid mortality rate of 4.3% (6/140), a statistically significant difference (p = 0.032).

COVID-19 Mortality and Pandemic Time Window. Both in BC patients and the reference group, Covid-19 mortality occurred mostly during the first two trimesters of 2020: 27.6% for the reference group and 75.9% for the BC group (p <0.001), Table 4.

Covid-19-related comorbidity conditions. Non-BC-related comorbidities in our patient group are displayed in Table 5. It can be seen that hypertension, diabetes mellitus, respiratory diseases, and increased BMI are quite prevalent.

COVID-19 Epidemiological Factors (Table 1)

Age. The mean age of BC patients with a CoT was 65 ±13(SD) years, with a range of 25-101 years.

Dwelling. 93.9% of BC patients lived in their own homes, and 6.1% at a nursing home

Clinical Presentation. Out of the 137 BC with a positive CoT, 16.1% were asymptomatic, 57.7% had mild symptoms, and 26.3% had pneumonia. Of those living at home, 20.5% were admitted to hospital, while of those living in a nursing home 25% were admitted (p =0.421). Hospital admissions amounted to 21.2% of BC patients with a positive CoT.

DISCUSSION

Covid-19 hospital admissions have been a matter of debate in our context, especially when elderly patients living in nursing homes were concerned. The overall admission rate in our survey of covid19- positive BC patients was 21%, which compares with the much higher rate of 47% in the study by Vuagnat et al in Paris[12], and 48% in the CCC19 study[4]. Notably, only a quarter of Covid-19-infected nursing home BC patients in our study were finally admitted to the hospital.

The Covid-19 mortality rate in our BC cohort was 11.7%, which is similar to the rate reported by the CCC19 consortium of 9% at 30 days[4]. Our mortality rate

was higher than the reported cumulative mortality figure for the feminine Catalan population over 20 years of age in the same period, which was 3.6%[17].

Covid-19 mortality in patients with BC seems to concentrate mainly on subjects over 70, as already reported[4,18], even though the most hard-hit age tier was for patients over 80. For BC patients under 70, mortality rates were considerably lower, just as has been reported for the general feminine Catalan population[17]. Of the several comorbid conditions considered in epidemiological studies and predictive models, age has been shown the most significant independent factor for Covid-19 infection and mortality compared with the rest: body weight (patients with a BMI over 25 shows significantly higher mortality), hypertension, type II diabetes, cancer, dementia, heart disease, autoimmune disease, or other respiratory conditions such as asthma. Of note, neither cigarette smoking nor alcohol intake was related to increased Covid mortality in BC patients[19]. Other factors unrelated to Covid mortality were the BC stage at the time of operation, local recurrence, and a diagnosis of infiltrating carcinoma versus intraductal carcinoma. Covid-19 mortality in our study group was conspicuously higher for patients living in nursing homes, albeit with no differences when compared with the reference group. These are figures pretty similar to the reported 38.7% rate by a Connecticut study[20] and lead us to consider that the fact of being a nursing home resident is in itself the most significant factor for Covid-19 mortality in BC patients.

Some authors have suggested that Coivid-19 mortality differences are linked to BC-related conditions, such as immunosuppression or metastatic spread[19] In our study, metastatic disease has proved to be the most significant cancer comorbidity factor for Covid-19 mortality. Of note, neither chemotherapy nor the time elapsed between BC diagnosis and Covid-19 infections has been associated with increased mortality, suggesting that patients treated with chemotherapy in our series did not have substantial immunosuppression for long enough to render covid-19 more deadly. Although lack of hormone therapy was a significant variable according to our multivariate analysis, it seems to be related only to the negative hormone receptor status in patients with subtypes Her2 and TN, which are also associated with higher rates of distant metastases.

In short, BC patients living in their own homes without distant metastases are at the same risk for Covid death as the general population.

Limitations. Because ours was a rather short and fixed data collecting time window from December 1, 2020, to March 30, 2021, this has resulted in a rather standard cross-sectional study where any inference may be difficult to apply. Both incidence and prevalence of Covid-19 change as the pandemic evolves and are dependent on the number of patients being considered over time. During that particular time window, some conversion from negative to positive CoT tests might have happened that could have had an impact on our results. Unfortunately, our database does not thoroughly include medical comorbid conditions unrelated to breast cancer that might have influenced covid-19 incidence and mortality results.

Comment. According to our multivariate analysis, distant metastases and living in a nursing home are the only independent predictive factors for Covid-19 mortality in BC patients.

Acknowledgments. We wish to thank Mr. Manel Martori for helping us with the graphic design, to the members of the Breast Unit, and finally to the staff of the Breast Cancer Screening Unit: Cristina, Sandra, and Clara; all of whom were essential contributors to keeping our breast cancer database updated.

Statements and Declarations

The authors have no relevant financial or non-financial interests to disclose.

Conflicts of interest: None

Author Contributions

"All authors contributed to the study conception and design as well as to Material preparation, data collection, and analysis. The first draft of the manuscript was written by [Carolina Chabrera] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

Data Availability

Data from the general population can be found at https://www.idescat.cat/pub/?id=covid.

Data from our study of patients are not available in the public domain, however, they can be accessed under the request of Doctor Antonio García-Fdez, who is responsible for the database of the Breast Unit at the Hospital Universitari Mútua de Terrassa. (drgarciafdez@hotmail.com)

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Hospital Universitari Mutua de Terrassa Review Board (Date July 12 2020, Nº O/21-094)

Consent to participate and publication

All patients gave their written consent shortly before breast surgery so that their anonymized individual data, including those from clinical follow-up, could be used for scientific purposes.

References:

1 WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Geneva: World Health Organization, March 11, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-mediabriefing-on-COVID-19---11-march-2020 (accessed April 20, 2020).

2 Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21: 335–37. https.// doi: 10.1016/S1470-2045(20)30096-6

3. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. Cancer Discov 2020; https://doi:10.1158/2159–8290.CD-20–0422.

4. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. COVID-19 and Cancer Consortium.Lancet. 2020 Jun 20;395(10241):1907-1918. https:// doi: 10.1016/S0140-6736(20)31187-9. Epub 2020 May 28.

5. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335–7.https://doi.org/10.1016/S147-2045(20)30096-6

6.Yu, J., Ouyang, W., Chua, M.L.K., and Xie, C. (2020). SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in wuhan, China. JAMA Oncol. https://doi.org/10.1001/jamaoncol.2020.0980.

7. Grasselli, G., Zangrillo, A., Zanella, A., et al. (2020). Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region, Italy. J. Am. Med. Assoc. *323*, 1574–1581.https:// doi.org/10.1001/jama.2020.5394

8. Argenzian, M.G., Bruc, S.L., Slate, C.L., et al. (2020). Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New

York: retrospective case series. BMJ *369*, m1996.
https://doi.org/10.1136/mbj.m1996

9. Richardson, S., Hirsch, J.S., Narasimhan, M., et al. (2020). Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA. 2020;323(20):2052-2059. https://doi.org/10.1001/jama.2020.6775

10. Marra A, Generali D, Zagami P, et al. Seroconversion in patients with cancer and oncology health care workers infected by SARS-COV-2. Annals of Oncology 2020;32(1):113-119.

11. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clinicians 2018;68:394–424. https://doi.org/10.3322/caac.21492

12. Vuagnat P, Frelaut M, Ramtohul T, et al. COVID-19 in breast cancer patients: a cohort at the Institut Curie hospitals in the Paris area. Breast Cancer Res 2020;22:55. https://doi.org/10.1186/s13058-020-01293-8

13. Sheng Z, Zhang L, Liu X, et al. Prognosis of COVID-19 in patients with breast cancer: A protocol for systematic review and meta-analysis**.** Medicine (Baltimore). 2020 Jul 31; 99(31): e21487.
https://doi.org/10.1097/MD.0000000000021487

14. Rosenbaum L: Facing COVID-19 in Italy - ethics, logistics, and therapeutics on the epidemic's front line. N Engl JMed: NEJMp2005492, 2020. PMID: 32187459. https doi.org/:10.1056/NEJMp2005492

15. Singh MK, Mobeen A, Chandra A, Joshi S, Ramachandran S. A meta-analysis of comorbidities in COVID-19: Which diseases increase the susceptibility of SARS-CoV-2 infection? Computers in Biology and Medicine Volumen 130, March 2021, 104219. https: doi.org/10.1016/j.compbiomed.2021.

104219.

16. Bialek S , Boundy E, Bowen V, et al. CDC. COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 343–46. https://doi.org/ 10.15585/mmwr.mm6912e2

17. Institut d'estadistica de Catalunya. https://www.idescat.cat. https://www.idescat.cat/novetats/?id=3972. https://www.idescat.cat/pub/?id=covid.

18. Inwald EC, Ortmann O, Koller M, Zeman F, Hofstädter F, Evert M, Brockhoff G and Klinkhammer-Schalke M: Screeningrelevant age threshold of 70 years and older is a stronger determinant for the choice of adjuvant treatment in breast cancer patients than tumor biology. Breast Cancer Res Treat *163*: 119-130, 2017. PMID: 28205042. DOI: 10.1007/s10549-017-4151-6

19. Incerti D, Rizzo S, Li X, Lindsay L, Yau V, Keebler D, Chia J, Tsai L.Prognostic model to identify and quantify risk factors for mortality among hospitalised patients with COVID-19 in the USA. BMJ Open. 2021 Apr 7;11(4):e047121. doi: 10.1136/bmjopen-2020-047121.

20. Yue Li, PhD,* Helena Temkin-Greener, PhD,* Gao Shan, MS,† and Xueya Cai, PhD† COVID-19 Infections and Deaths among Connecticut Nursing Home Residents: Facility Correlates JAGS 68:1899-1906, 2020

Table 1. Comorbidity factors for COVID-19 infection in our group of BC patients

	Covid negative	**Covid positive**	**p-value**
	N (%)	**N (%)**	
Age			0.635
<50	107/121 (88.4)	14/121 (11.6%)	
50-69	465/532 (87.4)	67/532 (12.6%)	
≥ 70	334/390 (85.6)	56/390 (14.4%)	
Smoker			0.039
No o ex >10 years	679/791 (85.8)	112/791 (14.2%)	
yes	217/240 (90.4%)	23/240 (9.6%)	
Alcohol intake			0.058
No	664/773 (85.9%)	109/773 (14.1%)	
yes	232/258 (89.9%)	26/258 (10.1)	
BMI			0.067
< 25	320/357 (89.6)	37/357 (10.4%)	
≥ 25	534/620 (86.1)	86/620 (13.9)	
pTNM			0.617
pTis	79/95 (83.2)	16/95 (16.8%)	
I	408/466 (87.6)	58/466 (12.4%)	
IIA	196/226 (86.7)	30/226 (13.3%)	
IIB	102/120 (85)	18/120 (15%)	

III*	116/130 (89.2)	14/130 (10.8%)	
Histologic Diagnosis			0.167
DCIS	79/95 (83.2)	16/95 (16.8%)	
Invasive Ca	827/948 (87.2)	121/948 (12.8%)	
Phenotype			0.110
Luminal A	319/361 (88.4)	42/361 (11.6)	
Luminal B (her2+/-)	395/477 (88.4)	52/447 (11.6)	
Pure Her2	35/42 (83.7)	7/42 (16.3)	
Triple Negative	79/99 (79.8)	20/99 (20.2)	
Local recurrence			
No	821/946 (86.8)	125/946 (13.2)	0.397
Yes	84/95 (88.4)	11/95 (11.6)	
Distant recurrence			0.531
No	863/994 (86.8)	131/994 (13.2%)	
Yes	43/49 (87.8)	6/49 (12.2%)	
Chemotherapy			0.472
No	410/473 (86.7)	63/473 (13.3)	
Yes	496/570 (87)	74/570 (13)	
Hormone therapy			0.007
No	115/144 (79.9)	29/144 (20.1%)	
Yes	791/899 (88)	108/899 (12.0%)	
Dwelling			<0.001
Home	862/979 (88.1)	117/979 (11.9)	
Nursing home	44/60 (66.7)	20/60 (33.3%)	
Months from BC diagnosis			0.045
≤ 60 months	294/326 (90.2)	32/326 (9.8%)	
61 to 120 months	247/296 (83.5)	49/296 (16.5%)	
>120 monts	365/421 (86.7)	56/421 (13.3%)	

Table 2. COVID-19 mortality related factors

	Alive	**Death from COVID-19**	**p-value**
	N (%)	**N (%)**	
Age			0.022
<50	120/121 (99.2)	1/121 (0.8)	
50-69	528/532 (99.2)	4/532 (0.8)	
≥70	379/390 (97.2)	11/390 (2.8)	
Smoker			0.024
No o ex >10 years	704/719 (97.9)	15/719 (2.1)	
yes	311/312 (99.7)	1/312 (0.3)	
Alcohol intake			0.010
No	757/773 (97.9)	13/773 (2.1)	
yes	258/258 (100)	0/258 (0)	
BMI			0.034
< 25	355/357 (99.4)	2/357 (0.6)	
≥ 25	606/620 (97.7)	14/620 (2.3)	
pTNM			0.924
pTis	91/92 (98.9)	1/92 (1.1)	
I	459/465 (98.7)	6/465 (1.3)	
IIA	224/227 (98.7)	3/227 (1.3)	
IIB	118/120 (98.3)	2/120 (1.7)	
III*	127/130 (97.7)	3/130 (2.3)	
Histologic Diagnosis			0.564
DCIS	94/95 (98.9)	1/95 (1.1)	
Ca Invasive	933/948 (98.4)	15/948 (1.6)	
Phenotype			0.031
Luminal A	355/361 (98.3)	6/361 (1.7)	
Luminal B (her2+/-)	444/447 (99.3)	3/447 (0.7)	
Pure Her2	41/42 (97.6)	1/42 (2.4)	
Triple Negative	94/99 (94.9)	5/99 (5.1)	
Local recurrence			0.436
No	934/948 (98.5)	14/948 (1.5)	
Yes	93/95 (97.9)	2/95 (2.1)	
Distant recurrence			0.034
No	982/995 (98.7)	13/995 (1.3)	
Yes	45/48 (93.5)	3/48 (6.5)	
Radiation Therapy			0.476

No	174/176 (98.8)	2/176 (1.2)	
Yes	853/867 (98.4)	14/867 (1.6)	
Chemotherapy			0.445
No	464/472 (98.3)	8/472 (1.7)	
Yes	563/571 (98.6)	8/571 (1.4)	
Hormone therapy			0.015
No	138/144 (95.8)	6/144 (4.2)	
Yes	889/899 (98.9)	10/899 (1.1)	
Dwelling			<0.001
Living place	971/979 (99.2)	8/979 (0.8)	
Geriatric residence	56/64 (87.5)	8/64 (2.5)	
Months from BC diagnosis			0.145
≤ 60 months	324/326 (99.4)	2/326 (0.6)	
61 to 120 months	292/296 (98.6)	4/296 (1.4)	
>120 months	411/421 (97.6)	10/421 (2.4)	

Table 3. Positive test cases and Mortality in the reference group and in the study group, according to age echelon.

	Reference group*				Study group			
Age	Confirmed cases		Covid Mortality		Confirmed cases		Covid Mortality	
Years	N	%	N	%	N	%	N	%
<50	94,652	6,1	74	0.1	14/121	11.6	1/14	7.1
50-59	31,347	5,7	160	0,5	32/247	13	2/32	6.3
60-69	19,411	4,4	352	1,8	35/285	12.3	2/35	5.7
70-79	14,097	4,1	1.061	7,5	33/245	13.5	4/33	12.1
80-89	16,073	7,4	7.130	26,5	19/119	16	7/23	30.4
≥90	10,863	16,5			4/26	15.4		
Overall	186.443	7.1	8.777	4.7	137/1043	13.1	16	11.7

*Source: Idescat.Ref

Table 4 COVID-19 mortality over five trimesters

	Reference group mortality				Study cohort mortality			
	Overall Control group		Nursing homes		Study cohort		Nursing homes	
Trimester	N	%	N	%	N	%	N	%
First 2020	1646/14433	11.4	664/1649	40.3	1/14	7.1	0/20	0
Second 2020	4806/29684	16.2	3339/9049	36.9	11/16	68.8	6/20	30
Third 2020	407/42923	0.9	188/1494	12.6	0/21	0	0/14**	0
Fourth 2020	1929/99839	1.9	847/5865	14.4	3/63	4.8	2/14**	14.3
First 2021	1724/80641	2.1	530/2758	19.2	1/23	4.3	0/12**	0
					16/137		8/20	

**Deaths from the previous trimester subtracted. *Source: Idescat Ref

Table 5. Epidemiological and clinical characteristics of BC patients who died from COVID-19

Nº	Age	Dwelling	Hospital admission	Trimester	Presentation	Distant metastases	BMI	Comorbidity
1	73	home	yes	1T20	Pneumonia	no	32.0	HBP,TIIDM, Asthma
2	87	home	yes	2T20	Pneumonia	no	25.9	None
3	90	nursing home	no	2T20	Pneumonia	no	31.6	HBP, TII DM
4	79	nursing home	no	2T20	Pneumonia	no	24.2	Heart fail, COPD, R Arthritis
5	79	nursing home	yes	2T20	Pneumonia	no	24.2	HBP, TII DM
6	88	nursing home	yes	2T20	Pneumonia	no	27.5	HBP, Asthma, TII DM
7	80	home	yes	2T20	Pneumonia	no	40.8	HBP, TII DM, heart dis.
8	79	nursing home	no	2T20	Pneumonia	no	29.7	HBP, TII DM
9	65	home	yes	2T20	Pneumonia	no	26.2	None
10	53	home	yes	2T20	Pneumonia	yes	29.9	Mets
11	41	home	yes	2T20	Pneumonia	yes	33.7	Mets
12	87	nursing home	no	2T20	Pneumonia	no	27.0	HBP
13	59	home	yes	4T20	Pneumonia	yes	34.4	cig. smoker
14	76	nursing home	no	4T20	Pneumonia	no	32.0	dementia
15	85	nursing home	no	4T20	Pneumonia	no	29.7	HBP
16	69	home	yes	1T21	Pneumonia	no	26.3	Recurrent Myeloma
Mean or %		38% nursing home. 62% home	38% no admission		100% pneumonia	19% yes metastasis		94% yes morbidity

Table 6. Results from the Multiple regression mortality factors analysis based on significant variables from the univariate analysis

				95% C:I. for EXP (OR)	
	Constant	Signific	OR	Lower	Upper
Distant Metastases	2,097	0.007	8.143	1,785	37,148
Hormone Therapy	-1,360	0.019	0,257	0,083	0,797
Dwelling	2,611	0.000	13,616	3,410	54,376